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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1642	28

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/836,455	CHATTERJEE ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-80* is/are pending in the application.

4a) Of the above claim(s) *1-5,20-37,39,40,42,43 and 46-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-12, 14-19, 38, 41, 44, 45 and 57-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12 and 14-80* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

1. The amendment filed December 4, 2001 (Paper No. 26) is acknowledged and has been entered. Claims 14-17, 41, 57, and 58 have been amended. Claims 74-80 have been added.

2. At Applicants' request, the amendment filed October 3, 2000 (Paper No. 23) is acknowledged and has been entered. Claims 68 and 69 are added. Claims 72 and 73 have been added.

3. At Applicants' request, the amendment filed June 26, 2000 (Paper No. 19) is acknowledged and has been entered. Claims 6-12, 14, 15, 19, 38, 41, 44, and 45 have been amended. Claims 62-71 have been added.

4. For further clarification of the record, the amendment filed November 22, 1999 (Paper No. 16) has been entered. Claim 13 has been canceled. Claims 6-12, 14-19, 38, 41, 44, and 45 have been amended. Claims 59, 60, and 61 have been added.

5. Claims 1-12 and 14-80 are pending in the application. Claims 1-5, 20-37, 39, 40, 42, 43, and 46-56 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14.

6. Claims 6-19, 38, 41, 44, 45, 57, and 58-80 are currently under prosecution.

Election/Restrictions

7. Applicants' requested rejoinder of presently excluded method claims in Paper No. 16, but as noted in the previous Office Action mailed April 24, 2001 (Paper No. 24), Applicants did not specifically identify the claims to which they were referring in the request for rejoinder. In reply to the Office Action mailed April 24, 2001 Applicants

state, "Applicants need not refer to specific claim numbers in order to identify method claims" and "[a]n example of such claims may be found in claims 67-69 [...], for which Applicants request rejoinder upon allowance of composition claims" (page 6, paragraph 4).

In reply to Applicants' remarks in Paper No. 26, first it is noted that as of the filing date of Paper No. 16, in which the request for rejoinder of unnamed claims was made, there were no method claims pending in the application, which had not been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention. Secondly, it is again noted that Applicants elected an invention in Paper No. 14 without traverse. Thirdly, there appear to not to have been any method claims in application, which incorporated all of the limitations of any of the claims directed to compositions, at the time the request for rejoinder was made. With respect to the claims referred to by Applicants' exemplary remark in Paper No. 26, it is noted that claims 67-69 were added by the amendment filed June 26, 2000 (Paper No. 19), after the request for rejoinder was made, so the request for rejoinder could not have included to those claims.

Nonetheless, in Paper No. 26, Applicants request rejoinder of claims 67-69 with the claims of the elected invention. Claims 67-69 are drawn to a method for preparing a polypeptide, said method comprising expressing the polynucleotide of claim 6 in a host cell. Because the subject matter of claims 67-69 would not have been restricted away from the claims of the elected invention since the search necessary to examine the invention of claims 67-69 would not constitute a serious additional burden, claims 67-69 are joined with the elected invention.

Priority

8. In reply to the Office Action mailed April 24, 2001, Applicants have amended the specification to properly claim the benefit of the filing date of Application No. PCT/US96/20757, which was filed December 19, 1996, which claims the benefit of the filing date of utility patent application US Serial No. 08/766,350, which was filed December 13, 1996, which claims the benefit of the filing date of provisional application

US Serial No. 60/035,345, which was filed January 29, 1996, and also claims the benefit of the filing date of provisional application US Serial No. 60/031,306, which was filed December 20, 1995.

Oath/Declaration

9. In the Office Action mailed April 24, 2001, it was noted that the declaration inaccurately records the filing date of priority document provisional application US Serial No. 60/035,345 and requires that a substitute declaration be filed, which is fully compliant with 37 CFR § 1.67(a).

In reply to the Office Action mailed April 24, 2001 Applicants do not comply with the requirement to file a substitute declaration and state, "Applicants believe that since the originally filed declaration accurately identifies the priority application, it meets the statutory requirements and therefore does not need to be re-executed" (page 8, paragraph 2). However, Applicants admit that there is "clerical inaccuracy in the declaration with respect to the date that this provisional application was filed" (page 8, paragraph 2).

In response to Applicants' remarks in Paper No. 26, it is clear that Applicants are knowledgeable of the inaccuracy in the declaration originally filed with the application and because Applicants have declared "that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true", Applicants may wish to reconsider their decision to traverse the requirement made in the Office Action mailed April 24, 2001 to replace the defective declaration. Nevertheless, if Applicants persist in traversing the requirement, for the record, it is clear that the application to which Applicants claim the benefit of its earlier filing date is provisional application US Serial No. 60/035,345, which was filed January 29, 1996, despite the fact that the current and originally filed declaration incorrectly records its filing date as January 26, 1999.

Objections for Lack of Compliance with the S quence Rules

10. The communication filed June 12, 1998 is not fully responsive to the Office communication mailed May 8, 1998 for the reason(s) set forth on the attached Notice To Comply With The Sequence Rules or CRF Diskette Problem Report. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

Since the reply appears to be *bona fide* attempt to comply with the requirements of the sequence rules (37 CFR §§ 1.821 - 1.825), Applicants are given the period of time within which to reply to this Office Action to correct the deficiency so as to comply with the sequence rules (37 CFR §§1.821 - 1.825) in order to avoid abandonment of the application under 37 CFR 1.821(g).

It is noted that the specification discloses in the third paragraph on page 69 that there are errors in the amino acid sequence; however, in the Brief Description of the Drawings, the specification discloses "Figure 1 depicts [...] the amino acid sequence (SEQ ID NO:2) of the light chain variable region of 11D10 and adjoining residues (page 5, lines 21 and 22). As noted on the attached Notice to Comply, the amino acid sequence of SEQ ID NO: 2 does not match the amino acid sequence aligned with SEQ ID NO: 1 or the amino acid sequence of SEQ ID NO: 2 in the Sequence Listing; therefore the application is not compliant with the Sequence Rules set forth in 37 CFR §§ 1.821 - 1.825. Although the specification discloses the presence of errors in the amino acid sequence, the lack of correspondence in the sequences depicted in the figures and the Sequence Listing is unacceptable.

Claim Rejections Withdrawn and Response to Applicants' Remarks

11. In the Office Action mailed May 17, 1999 (Paper No. 15), claims 6-19, 38, 41, 44, 45, 57, and 58 were rejected under 35 USC §112, second paragraph. In response to the Office Action Applicants canceled claim 13 and amended claims 6-12, 14-19, 38, 41, 44, and 45 to satisfactorily resolve the issues raised in the Office Action. Accordingly, at Applicants' request in Paper No. 26, the rejection of claims 6-19, 38, 41, 44, 45, 57, and 58 were rejected under 35 USC §112, second paragraph for the reason stated in Paper No. 15 is withdrawn.

12. In the Office Action mailed May 17, 1999 (Paper No. 15), claims 6-19, 38, 41, 44, 45, 57, and 58 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides that encode the entire variable regions of monoclonal antibody 11D10, does not reasonably provide enablement for vaccines or polynucleotides encoding only portions of the variable regions of monoclonal antibody 11D10, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. In reply to the Office Action, Applicants canceled claim 13 and amended claims 6-12, 14-19, 38, 41, 44, and 45 so that the claims are no longer encompass vaccines; and therefore to the extent that vaccines were at issue in the rejection, the rejection of the claims under 35 USC § 112, first paragraph is withdrawn. However, the claims still encompass polynucleotides comprising a sequence that encode a polypeptide comprising an immunoglobulin variable region that contains either the three light chain complementarity determining regions (CDRs) or the three heavy chain CDRs of the monoclonal antibody 11D10, which is capable of eliciting an anti-HMFG immunological response in a mammal. Consequently, the claims still encompass polynucleotides that encode only a portion of the monoclonal antibody. Therefore, at least part of the basis of the rejection made in the Office Action mailed May 17, 1999 is still applicable to the present claims; nonetheless, it appears that the rejection of claims 6-12, 16-19, 38, 41, 44, and 45 was withdrawn in the Office Action mailed April 24, 2001 (Paper No. 24), although no reason for the withdrawal was stated. A new claims rejection under 35 USC § 112, first paragraph, which includes claims 6-12, 16-19, 38, 41, 44, and 45, is made in this Office Action, because despite that the rejection of claims 6-12, 16-19, 38, 41, 44, and 45 was withdrawn in Office Action mailed April 24, 2001, the issues raised in the Office Action mailed May 17, 1999 have yet to be satisfactorily resolved in total.

13. In the Office Action mailed May 17, 1999 (Paper No. 15):

(a) Claims 6, 8, 10, 12, 13, 15-17, 19, 38, 41, 44, and 58 were rejected under 35 USC § 102(b) as being anticipated by Mo, et al.

(b) Claims 6, 8, 10, 12, 13, 15-17, 19, 38, 41, 44, and 58 were rejected under 35 USC § 102(e) as being anticipated by US Patent No. 5,808,033-A (Gourlie, et al).

(c) Claims 6, 8, 10, 12, 13, 15-17, 19, 38, 41, 44, and 58 were rejected under 35 USC § 102(b) as being anticipated by Liu, et al or De Waele, et al.

(d) Claims 6-9, 11, 14, 16, 17, 38, 41, 44, and 57 were rejected under 35 USC § 102(b) as being anticipated by Shlomchik, et al, Kavaler, et al, Seidman, et al, or Darsley, et al.

(e) Claims 6, 7, 9, 11, 13, 14, 16, 17, 19, 38, 41, 44, and 57 were rejected under 35 USC § 102(e) as being anticipated by US Patent No. 5,840,299-A (Bendig, et al).

In reply to the Office Action Applicants canceled claim 13 and amended claims 6-12, 14-19, 38, 41, 44, and 45 to obviate the basis of each of the rejections. Accordingly, at Applicants' request in Paper No. 26, each of the above rejections of the claims under 35 USC § 102(b) or 102(e), which were made for the reasons stated in Paper No. 15, is withdrawn.

14. In the Office Action mailed May 17, 1999 (Paper No. 15), claims 16, 17, 19, and 44 were rejected under 35 U.S.C. 102(b) and in the Office Action mailed April 24, 2001 (Paper No. 24), claims 16-19, 44, and 45 were rejected under 35 U.S.C. 102(b) as being anticipated by Bhattacharya, et al (*Cancer Immunology & Immunotherapy* **38**: 75-82, 1994), Chakraborty, et al (*Proceedings of the American Association for Cancer Research* **35**: 497, Abstract No. 2963), or Bhattacharya-Chatterjee, et al (In *Antigen and Antibody Molecular Engineering in Breast Cancer Diagnosis and Treatment,* Ceriani, RL, Ed., Plenum Press: New York, pp. 139-148, 1994). However, it is noted that the claims 16 and 17 were drawn to a polynucleotide according to claim 6, wherein the polynucleotide is a cloning vector or an expression vector, respectively, and are presently drawn to a cloning vector or an expression vector comprising the polynucleotide according to claim 6, but none of the cited references teach a polynucleotide according to claim 6, which is a vector, or a vector comprising the

polynucleotide of claim 6. Also, none of the cited references teach the expression vector of claim 17, wherein the expression vector is vaccinia. Similarly, none of the cited references teach a host cell comprising the polynucleotide of claim 6, wherein the polynucleotide is recombinant, as claim 19 presently recites. Furthermore, none of the cited references teach the immunogenic composition of claim 41, wherein the polynucleotide is comprised in a live virus or viral expression vector, wherein the expression vector is vaccinia. Therefore, the teachings of Bhattacharya, et al, Chakraborty, et al, and Bhattacharya-Chatterjee, et al, do not anticipate the claimed invention. Accordingly, the rejections of claims 16-19, 44, and/or 45 under 35 USC § 102(b) as being anticipated by Bhattacharya, et al, Chakraborty, et al, or Bhattacharya-Chatterjee, et al for the reasons stated in Paper Nos. 15 and 24 are withdrawn.

15. In the Office Action mailed May 17, 1999 (Paper No. 15), claims 6-17, 19, 38, 41, 44, 57, and 58 were rejected under 35 USC § 102(f) because in view of Chatterjee, et al or Chakraborty, et al, it appears that the Applicants did not invent the claimed subject matter. In reply to the Office Action, Applicants submitted a copy of a declaration filed under 37 CRF § 1.132 by co-inventor Mayala Bhattacharya-Chatterjee during the prosecution of related and co-pending US Application Serial No. 08/766,350, in which it was stated that Ewe Mrozek, Sonjoy Mukerjee, Mala Chakraborty, and M. Sherratt, although assisting in experiments related to the invention, worked under the direct supervision of Mayala Bhattacharya-Chatterjee and did not make independent contributions to the generation of monoclonal antibody 11D10, and further stated that Roberto Ceriani and Heinz Kohler did not participate in or make any contributions to the generation and characterization of monoclonal antibody 11D10. It is noted that the individual in question is A.J. Sherratt and not M. Sherratt, to whom the declaration refers. Nevertheless, despite the fact that the present claims are drawn to polynucleotides that encode monoclonal antibody 11D10, and not the monoclonal antibody *per se*, since the references cited as the basis of the rejection do not disclose or suggest that the claimed polynucleotides had been cloned or sequenced by the authors of those references, Applicants' declaration is deemed sufficient to overcome

the basis of the rejection of the claims under 35 USC § 102(f). Therefore, at Applicants' request, the rejection of claims 6-17, 19, 38, 41, 44, 57, and 58 under 35 USC § 102(f) for the reasons stated in the Office Action mailed May 17, 1999 is withdrawn.

16. In the Office Action mailed May 17, 1999 (Paper No. 15), claim 19 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claim 3 of co-pending US Application Serial No. 08/766,350. In reply to the Office Action, Applicants amended claim 19 to recite the limitation "wherein the polynucleotide is a recombinant polynucleotide", thus obviating the provisional basis of rejection. Accordingly, at Applicants' request in Paper No. 26, the provisional rejection of claim 19 under the judicially created doctrine of obviousness-type double patenting for the reason stated in Paper No. 15 is withdrawn.

17. In the Office Action mailed April 24, 2001 (Paper No. 24):

(a) Claims 15 and 58 were rejected under 35 USC § 102(b) as being anticipated by Mo, et al, Liu, et al, or De Waele, et al.

(b) Claims 15 and 58 were rejected under 35 USC § 102(e) as being anticipated by US Patent No. 5,808,033-A (Gourlie, et al).

(c) Claims 14 and 57 were rejected under 35 USC § 102(b) as being anticipated by Shlomchik, et al, Kavaler, et al, Seidman, et al, or Darsley, et al.

(e) Claims 15 and 58 were rejected under 35 USC § 102(e) as being anticipated by US Patent No. 5,840,299-A (Bendig, et al).

In reply to the Office Action Applicants have amended claims 14-17, 41, 57, and 58 to obviate the basis of each of the rejections. Accordingly, each of the above rejections of the claims under 35 USC § 102(b) or 102(e), which were made for the reasons stated in Paper No. 24, is withdrawn.

18. In the Office Action mailed April 24, 1999 (Paper No. 24), claims 14, 15, 57, 58, 72, and 73 were rejected under 35 U.S.C. 112, first paragraph for the reason stated in the Office Action mailed May 17, 1999 (Paper No. 15), because the specification, while

being enabling for polynucleotides that encode the entire variable regions of monoclonal antibody 11D10, does not reasonably provide enablement for polynucleotides encoding only portions of the variable regions of monoclonal antibody 11D10, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Office Action mailed April 24, 2001 stated the reason for the rejection is that the amount of guidance, direction, and exemplification disclosed in the specification is not reasonably commensurate in scope with the claims. Therefore, because the unpredictability and state of the art, as discussed in the Office Action mailed May 17, 1999, one skilled in the art could not make and/or use the claimed invention with a reasonable expectation of success without need to perform undue experimentation. Consequently, the specification fails to the meet the enablement requirement of 35 USC § 112, first paragraph.

In reply to the Office Action, Applicants traverse the rejection of the claims under 35 USC § 112, first paragraph arguing:

(1) The Examiner appears to have misconstrued the claims (paragraph bridging pages 8 and 9).

(2) Contrary to the position taken by the Office, the scope of the claims is commensurate with what is disclosed in the specification (page 9, paragraph 2).

(3) The specification clearly enables and provides adequate written description for the claimed invention (paragraph bridging pages 9 and 10).

(4) The specification teaches how to make and use the invention claimed in claims 72 and 73 (page 10, paragraph 2).

In response to Applicants' arguments, although the Examiner appears to have inaccurately described the claims, it does not appear that Examiner misconstrued the scope of the claims. As Applicants note, although claims 14 and 15 are drawn to "a polynucleotide comprising a region of [...] the sequence contained in SEQ ID NO:1" and SEQ ID NO: 3, respectively, SEQ ID NO: 2 and SEQ ID NO: 4 are amino acid sequences encoded by the polynucleotide sequences of SEQ ID NO: 1 and SEQ ID

NO: 3, respectively. Therefore, it is accurate to state that the claims encompass polynucleotides comprising a region of the sequence that encodes either the light chain or the heavy chain of the monoclonal antibody 11D10. While Applicants assert, contrary to the position taken by the Office, the scope of the claims is commensurate with what is disclosed in the specification, Applicants do not discuss the factual basis for their assertion.

Nonetheless, Applicants further assert the specification clearly enables and provides adequate written description for the claimed invention. Applicants state that "methods of preparing polynucleotides are extensively disclosed in the specification" and "[t]hese polynucleotides can be used in a variety of ways, as described throughout the specification" (paragraph bridging pages 9 and 10). This argument is persuasive, given the polynucleotide sequences of SEQ ID NO: 1 and SEQ ID NO: 3, one skilled in the art would have a reasonable expectation of making and using the claimed invention as a probe to detect or quantify a nucleic acid molecule comprising a polynucleotide sequence encoding a variable region of the monoclonal antibody 11D10. Therefore, the rejection of claims 14, 15, 57, 58, 72, and 73 under 35 U.S.C. 112, first paragraph for the reason stated in the Office Action mailed May 17, 1999 is withdrawn.

19. In the Office Action mailed May 17, 1999 (Paper No. 15) claims 6-17, 19, 38, 41, 44, 57, and 58 were rejected under 35 U.S.C. 102(b) as being anticipated by Chakraborty, et al (*Journal of Immunotherapy* **18**: 95-103, 1995) and in the Office Action mailed April 24, 2001 (Paper No. 24), claims 6-12, 16-19, 38, 41, 44, 45, 59-66, and 70-72 were rejected under 35 U.S.C. 102(b) as being anticipated by Chakraborty, et al (*Journal of Immunotherapy* **18**: 95-103, 1995). These rejections are improper, because the reference cited is not prior art under 35 USC § 102(b); therefore the rejections of the claims under 35 USC § 102(b) as being anticipated by Chakraborty, et al for the reasons stated in the Paper Nos. 15 and 24 are withdrawn.

20. In the Office Action mailed April 24, 2001 (Paper No. 24), claims 64-66 and 71 were rejected under 35 U.S.C. 102(b) as being anticipated by Bhattacharya, et al

(*Cancer Immunology & Immunotherapy* **38**: 75-82, 1994), Chakraborty, et al (*Proceedings of the American Association for Cancer Research* **35**: 497, Abstract No. 2963), or Bhattacharya-Chatterjee, et al (In *Antigen and Antibody Molecular Engineering in Breast Cancer Diagnosis and Treatment,* Ceriani, RL, Ed., Plenum Press: New York, pp. 139-148, 1994). However, it is noted that the claims are drawn to a polynucleotide according to claim 6, which encodes an immunoglobulin variable region of both the light and heavy chains of monoclonal antibody 11D10, and the hybridoma that produces monoclonal antibody 11D10 does not comprise a single polynucleotide encoding both the immunoglobulin variable regions of the light and heavy chains of monoclonal antibody 11D10, because the immunoglobulin light and heavy chains are encoded by discrete genetic loci. Therefore, the hybridoma of Bhattacharya, et al, Chakraborty, et al, and Bhattacharya-Chatterjee, et al, although producing monoclonal antibody 11D10, does not anticipate the claimed invention. Furthermore, none of the cited references teach the immunogenic composition of claim 41, which is sterile. Accordingly, the rejection of claims 64-66 and 71 under 35 USC § 102(b) as being anticipated by Bhattacharya, et al, Chakraborty, et al, or Bhattacharya-Chatterjee, et al for the reason stated in Paper No. 24 is withdrawn.

21. In the Office Action mailed April 24, 2001 (Paper No. 24), claims 57 and 58 were rejected under 35 USC §101 because the claimed invention is directed to non-statutory subject matter; however, claims 57 and 58 are drawn to kits, which is statutory subject matter. Accordingly, the rejection of claims 57 and 58 under 35 USC § 101 for the reason stated in the Paper No. 24 is withdrawn.

Claim Rejections Maintained and Response to Applicants' Remarks

Claim Rejections – 35 USC § 101

22. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

23. Claims 14, 15, and 72-75 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter for the reason stated in the Office Action mailed April 24, 2001 (Paper No. 24).

Claims 14 and 15 are drawn to polynucleotides comprising a region of at least 100 or 75 contiguous residues of the sequence contained in SEQ ID NO: 1 or SEQ ID NO: 3, respectively. Claims 72-75 are drawn to polynucleotides encoding an immunoglobulin variable region containing the three light or heavy chain variable CDRs contained in SEQ ID NO: 2 or SEQ ID NO: 4, respectively.

Claims 14, 15, and 72-75 encompass a naturally occurring product. For example, the hybridoma that produces the monoclonal antibody 11D10, which is deposited under ATCC Accession No. HB-12020 naturally produces polypeptides that fulfill the limitations of the claims. Furthermore, the hybridoma is known to have been derived from a naturally occurring lymphocyte also produces the monoclonal antibody 11D10 and therefore also produces polypeptides that fulfill the limitations of the claims. However, as the claims are written, the subject matter of the claims cannot be distinguished from such naturally occurring products.

In Paper No. 26, Applicants traverse the rejection of the claims under 35 USC § 101 arguing that "this rejection is due to an erroneous assumption by the Office that the claimed polynucleotides are naturally-occurring" and "the polynucleotide sequences of the invention are not naturally-occurring in the sense that they arose due to manipulations to make an antibody-producing hybridoma, which does not occur in nature" (page 14, paragraph 5). In reply to Applicants' arguments, as stated above, although the hybridoma itself is not naturally occurring, the polynucleotides encompassed by the claims are naturally occurring in the sense that the polynucleotides are naturally produced by the hybridoma. Moreover, although fusing a lymphocyte with another cell produced the hybridoma, the lymphocyte also naturally produces polynucleotides encompassed by the claims, and the lymphocytes occur naturally in the immunized animal.

In traversing the rejection of the claims under 35 USC § 112, first paragraph, which was made in the Office Action mailed May 17, 1999, Applicants argued that because the Examiner stated in the claims rejections under 35 USC § 102 that "[o]ne of skill in the art would reasonably conclude that immunization with Mo et al.'s polypeptide would result in antibodies which also bind the 11D10 antibody" (Paper No. 19, page 8, paragraph 5), the present claims drawn to polynucleotides encoding the variable region of the light chain or heavy chain of monoclonal antibody 11D10 are necessarily enabled (Paper No. 19, page 9, paragraph 1). However, in response to Applicants' remarks, claims 14, 15, and 72-75, which are the subject of this rejection, are not drawn to polynucleotides encoding the variable region of the light chain or heavy chain of monoclonal antibody 11D10, but rather to polynucleotides comprising a region of at least 100 or 75 contiguous residues of the polynucleotide sequence contained in SEQ ID NO: 1 and SEQ ID NO: 3, respectively. The Examiner's statement in the Office Action mailed May 17, 1999 was made to support the basis of a rejection under 35 USC § 102. Because the claims recited the limitation "comprising a sequence encoding a polypeptide having immunological activity of monoclonal anti-idiotype antibody 11D10, wherein the polypeptide comprises at least five contiguous amino acids of a variable region of 11D10", then it is proper to cite any reference available as prior art in making a claim rejection under 35 USC §102, which teaches a polynucleotide comprising a sequence encoding a polypeptide, wherein the polypeptide comprises at least five contiguous amino acids of a variable region of 11D10. It would not be necessary that the reference teach that the polypeptide encoded by the claimed polynucleotide has the immunological activity of monoclonal anti-idiotype antibody 11D10, because such a property would be an inherent feature of any polynucleotide comprising a sequence encoding a polypeptide, wherein the polypeptide comprises at least five contiguous amino acids of a variable region of 11D10, according to the claim. For this reason, the statement made by the Examiner in the grounds of the 35 USC § 102 rejections should not be construed as factual evidence that the disclosure is sufficient to meet the enablement requirements of 35 USC §112, first paragraph. Additionally, in view of the 35 USC § 112, first paragraph rejection for lack of an enabling disclosure, which was

also made in the Office Action mailed May 17, 1999, it is evident that contrary to Applicants' assertion, the Examiner had reason to doubt Applicants' assertion that the claims were enabled by the disclosure. Finally, although the Examiner stated that the prior art polypeptides would "result in antibodies which also bind the 11D10 antibody", the Examiner did not state that the antibodies would bind the paratope of monoclonal antibody 11D10, or that the antibodies would specifically bind HMFG, or that the antibodies would have the immunological activity of monoclonal antibody 11D10, as the claims would have required.

Applicants' arguments have been carefully considered but not found persuasive. Therefore, the rejection of claims 14, 15, 72, and 73 under 35 USC § 101 for the reason stated in the Office Action mailed April 24, 2001 is maintained.

Amending claims 14, 15, 72, and 73 to recite, for example, the term "isolated", "purified", or "recombinant" before "polynucleotide" can obviate this rejection, because the recitation of such a limitation would serve to distinguish the subject matter of the claims from the naturally occurring products, which are presently encompassed by the claims but are not patentable under 35 USC § 101.

It is noted that Applicants remark that US Patent No. 5,934,821-A claims "polynucleotides which arose from production of a hybridoma", but the claims do not contain the term "isolated". As stated in the paragraphs above, the claims are not patentable under the statutory basis of 35 USC § 101 and Applicants' observation is therefore inconsequential.

Claim Rejections – 35 USC § 102

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

25. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

26. Claims 6-12, 14, 15, 38, 41, 57-63, 70, 72-80 are rejected under 35 U.S.C. 102(b) as being anticipated by Bhattacharya, et al (*Cancer Immunology & Immunotherapy* **38**: 75-82, 1994), Chakraborty, et al (*Proceedings of the American Association for Cancer Research* **35**: 497, Abstract No. 2963), Bhattacharya-Chatterjee, et al (In *Antigen and Antibody Molecular Engineering in Breast Cancer Diagnosis and Treatment,* Ceriani, RL, Ed., Plenum Press: New York, pp. 139-148, 1994), or Chakraborty, et al (*Journal of Immunotherapy* **18**: 95-103, 1995) for the reason stated in the Office Action mailed May 17, 1999 (Paper No. 15) and reiterated in the Office Action mailed April 24, 2001 (Paper No. 24).

Chakraborty, et al, Bhattacharya-Chatterjee, et al, and Chakraborty, et al teach monoclonal antibody 11D10, which is produced by a hybridoma. The polynucleotides encoding the light and heavy chains of monoclonal antibody 11D10 are inherent features of the hybridoma. Because the subject matter of the claims cannot be distinguished from the polynucleotides of which the hybridoma is composed, the teachings of Chakraborty, et al, Bhattacharya-Chatterjee, et al, and Chakraborty, et al anticipate the claimed invention. All the limitations of the claims are met.

In response to the Office Actions mailed May 17, 1999 (Paper No. 15) and April 24, 2001 (Paper No. 24) Applicants traverse the rejection arguing that since neither monoclonal antibody 11D10 nor the hybridoma that produces the monoclonal antibody

were publicly available before the effective filing date sought by Applicants in this application, although the references disclose the antibody, none of the references teach either the amino acid sequence of the antibody or the polynucleotide sequence of the polynucleotides encoding the antibody and therefore the references were not enabling of the claimed invention. To support their argument, Applicants have submitted a copy of a declaration filed under 37 CFR § 1.132 by Malaya Bhattacharya-Chatterjee during the prosecution of the related and co-pending US application Serial No. 08/766,350, which states: (a) the hybridoma and the antibody had been maintained exclusively under the control of the declarer, (b) there has been no free exchange of the hybridoma or the antibody, and (c) neither the hybridoma nor the antibody were released to the public before the filing of US application Serial No. 08/766,350 or US provisional application Serial No. 60/031,306. Furthermore, the declaration by Malaya Bhattacharya-Chatterjee states that none of Ewe Mrozek, Sonjoy Mukerjee, Mala Chakraborty, Roberto Ceriani, Heinz Kohler, and M. Sherratt distributed the antibody or the hybridoma to anyone outside of the laboratory. Additionally, Applicants have submitted a copy of a declaration filed under 37 CFR § 1.132 by Sunil K. Chatterjee during the prosecution of US application Serial No. 08/766,350, which states: (a) the hybridoma producing monoclonal antibody 11D10 was used in the declarer's laboratory under his strict and exclusive control, (b) no one in his laboratory took the antibody or the hybridoma and no one had permission to do so, (c) the public did not have access to the hybridoma or the antibody at any time before the filing date of US application Serial No. 08/766,350, and (d) the declarer did not make the antibody or hybridoma available to the public. Also, Applicants have submitted a copy of a declaration filed under 37 CRF § 1.132 by Kenneth A. Foon during prosecution of US application Serial No. 08/766,350, which states the public did not obtain the hybridoma or the antibody at any time before the filing date of US application Serial No. 08/766,350.

In response to Applicants' arguments, it is agreed that if neither the antibody nor the hybridoma producing the antibody were accessible or available upon request to any other individual that although the cited references disclose the antibody and therefore disclose the hybridoma, none of the cited references can be considered to provide an

enabling disclosure of the claimed invention. Consequently, the question that must be addressed is, whether or not someone other than the co-inventors had access or could have acquired upon request either the antibody or the hybridoma producing the antibody before the effective filing date sought by Applicants in this application, i.e., December 20, 1995?

While the declarations of the co-inventors attempt to address and answer this question, in particular response to the declaration by Malaya Bhattacharya-Chatterjee, it is noted that the declaration does not explicitly state how the hybridoma and the antibody were controlled by the declarer and although the declaration states that neither the hybridoma nor the antibody were distributed to any other party before the effective filing date sought by Applicants in this application, the declaration does not state that neither the hybridoma nor the antibody were publicly accessible or available upon request. With regard to the statements that none of Ewe Mrozek, Sonjoy Mukerjee, Mala Chakraborty, Roberto Ceriani, Heinz Kohler, and M. Sherratt distributed the antibody or the hybridoma to anyone outside of the laboratory, it is noted that this is hearsay evidence, which has not been supported by the declarations of any of Ewe Mrozek, Sonjoy Mukerjee, Mala Chakraborty, Roberto Ceriani, Heinz Kohler, or A.J. Sherrattt. Also, the declaration states that M. Sherratt did not distribute the antibody or the hybridoma to anyone outside of the laboratory, but A.J. Sherratt is the individual in question. Then, on page 5 of the declaration, it is stated, "[t]o the best of my knowledge and belief, the public **did** have access to the cell line" (emphasis added) (paragraph 1); although this is clearly the result of a typographical error, it is an error, nonetheless, that obscures the intent of the declaration.

In particular response to the declaration by Sunil K. Chatterjee, although the declaration states that the hybridoma producing monoclonal antibody 11D10 was used in the declarer's laboratory under his strict and exclusive control, the declaration does not explicitly state how the hybridoma and the antibody were controlled by the declarer. Furthermore, while the declarer stated that no one in his laboratory took the antibody or the hybridoma or had his permission to do so and that the public did not have access to the hybridoma or the antibody at any time before the filing date of this application, and

even though he did not make the antibody or hybridoma available to the public, the declaration does not state that the antibody or the hybridoma could not have been obtained upon request. Also, on page 3 of the declaration, it is stated, "[t]o the best of my knowledge and belief, the public **did** have access to the cell line" (emphasis added) (paragraph 3); although this is clearly the result of a typographical error, it is an error, nonetheless, that obscures the intent of the declaration.

In particular response to the declaration by Kenneth A. Foon, although the declaration states that monoclonal antibody 11D10 was used in clinical studies under the declarer's strict and exclusive control and states who had access to the antibody and to whom the antibody was given, the declaration does not explicitly state how the antibody was controlled by the declarer. Although the declaration states the public did not obtain the hybridoma or the antibody at any time before the filing date of US application Serial No. 08/766,350, the declaration does not state that neither the antibody nor the hybridoma were publicly accessible or attainable upon request.

Furthermore none of the declarations by any one of the co-inventors states that neither the monoclonal antibody 11D10 nor the hybridoma producing the monoclonal antibody was either publicly accessible or attainable upon request before the filing date of this application. Therefore, it cannot be ascertained whether or not the monoclonal antibody 11D10 or the hybridoma producing the monoclonal antibody were publicly accessible or attainable upon request during the interim between the filing date of the related and co-pending US application Serial No. 08/766,350 and the filing date of this application. Also, it is noted that the strain of hybridoma producing the antibody was deposited in the ATCC before the filing date of this application, but according to the deposit receipt dated February 6, 1996, the strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a US Patent is issued citing the strain, and the ATCC is instructed by the USPTO or the depositor to release the strain, and it appears that no US Patent citing the strain had issued before the filing date of this application.

With regard to Applicants' arguments, the present claims encompass polynucleotides, which occur naturally in the hybridoma producing the monoclonal

antibody. Therefore, although none of the cited references teach the polynucleotide sequences of the nucleic acid molecules contained in the hybridoma that encode the light and heavy chains of monoclonal antibody 11D10, contrary to Applicants' argument, the polynucleotides are inherent features of the hybridoma and one skilled in the art would not have to deduce the polynucleotide sequences of those nucleic acid molecules to possess the claimed invention. Nonetheless, if the antibody and/or the hybridoma producing the antibody were accessible or attainable upon request, the skilled artisan could readily determine the polynucleotide sequences of the nucleic acid molecules expressed in the hybridoma, which encode the light and heavy chains of monoclonal antibody 11D10, using conventional methodology that was routine at the time the invention was made. Thus, provided the antibody and/or the hybridoma were accessible or attainable, the cited references provided sufficient disclosure of the antibody and the hybridoma to enable one skilled in the art to deduce the polynucleotide sequences disclosed in this application without having to have the benefit of its disclosure, given sufficient motivation to do so. See the new rejection of the claims under 35 USC § 103(a) set forth below.

Consequently, Applicants' arguments and the declarations by the co-inventors have been carefully considered but have not been found persuasive, because the declarations are deficient in failing to adequately address the question of public accessibility and availability, upon request, of the monoclonal antibody and the hybridoma that produces the monoclonal antibody. Therefore, the rejections of claims 6-12, 14, 15, 38, 41, 57-63, 70, 72-80 under 35 U.S.C. 102(b) as being anticipated by Bhattacharya, et al, Chakraborty, et al, Bhattacharya-Chatterjee, et al, or Chakraborty, et al for the reasons stated in the Paper Nos. 15 and 24 are maintained.

However, amending claims 6, 14, 15, 72, and 73 to recite, for example, the term "isolated", "purified", or "recombinant" before "polynucleotide" can obviate this rejection, because the recitation of such a limitation would serve to distinguish the subject matter of the claims from the naturally occurring polynucleotides of the hybridoma that produces monoclonal antibody 11D10, which are presently encompassed by the claims.

N w Claim Objections

27. Claim 59 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form

Claim 59 is drawn to the polynucleotide of claim 6, but recites the phrase "wherein the antibody 11D10 has the light and heavy variable region sequences contained in SEQ ID NO:2 and SEQ ID NO:4, respectively". Because the amino acid sequences of the light and heavy variable region sequences of a monoclonal antibody are inherent to the antibody and because the amino acid sequences of the light and heavy variable region sequences of the monoclonal antibody are contained in SEQ ID NO: 2 and SEQ ID NO: 4, respectively, recitation of phrase in claim 59 does not further limit the antibody of claim 6 and therefore claim 59 does not further limit the subject matter of claim 6 from which it depends.

28. Claim 79 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

New Claim Rejections

Claim Rejections – 35 USC § 101

29. Claims 6-12, 59, 62, 63, and 72-75 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter for the reason stated in the Office Action mailed April 24, 2001 (Paper No. 24).

Claims 6-12 are drawn to a polynucleotide comprising a sequence encoding a polypeptide comprising the immunoglobulin light chain variable domain or the immunoglobulin heavy chain variable domain of monoclonal antibody 11D10. Claims 59, 62, and 63 are drawn to the polynucleotide of claim 6. Claims 72-75 are drawn to polynucleotides encoding an immunoglobulin variable region containing the three light

or heavy chain variable CDRs contained in SEQ ID NO: 2 or SEQ ID NO: 4, respectively.

Claims 6-12, 59, 62, 63, and 72-75 encompass a naturally occurring product. For example, the hybridoma that produces the monoclonal antibody 11D10, which is deposited under ATCC Accession No. HB-12020 naturally produces polypeptides that fulfill the limitations of the claims. Furthermore, the hybridoma is known to have been derived from a naturally occurring lymphocyte also produces the monoclonal antibody 11D10 and therefore also produces polypeptides that fulfill the limitations of the claims. However, as the claims are written, the subject matter of the claims cannot be distinguished from such naturally occurring products.

Amending claims 6, 72, and 73 to recite, for example, the term "isolated", "purified", or "recombinant" before "polynucleotide" can obviate this rejection, because the recitation of such a limitation would serve to distinguish the subject matter of the claims from the naturally occurring products, which are presently encompassed by the claims but are not patentable under 35 USC § 101.

30. Claims 14 and 15 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well-established utility.

Claims 14 and 15 are drawn to a polynucleotide comprising a region of at least 100 or at least 74 contiguous residues of the sequence contained in SEQ ID NO: 1 or SEQ ID NO: 3, respectively.

The specification asserts that the claimed invention can be used as a probe to detect or quantify a nucleic acid molecule comprising a polynucleotide sequence encoding a variable region of the monoclonal antibody 11D10, but this asserted utility lacks specificity and is not considered a substantial utility. Since such a utility generally applies to any nucleic acid molecule, the asserted utility for the invention is viewed as generic and trivial. It is common and routine to use a portion of a nucleic acid molecule as a probe to detect or quantify a nucleic acid comprising the polynucleotide sequence of the probe.

Otherwise, the specification asserts that the invention can be used to elicit an anti-HMFG immune response in a mammal to induce antitumor immunity in the mammal, but this asserted utility lacks credibility. Notably the specification does not disclose working exemplification of the use of the claimed invention to elicit an anti-HMFG immunological response in a mammal. In fact, the specification only demonstrates the use of an antibody to elicit an anti-HMFG immunological response in a mammal. While it is credible that a polynucleotide encoding a single-chain antibody derived from the amino acid sequences of which monoclonal antibody 11D10 is composed, upon expression in a mammal, would be capable of eliciting the same anti-HMFG immunological response that is elicited by the monoclonal antibody 11D10, it is not credible that any fragment of a polynucleotide consisting of at least 100 or at least 75 contiguous residues of SEQ ID NO: 1 or SEQ ID NO: 3, respectively, would be capable of doing so. There is no factual evidence in the specification that would support the asserted utility of the claimed invention; and for the reasons stated in the new grounds of rejection of the claims under 35 USC § 112, first paragraph, one skilled in the art would not accept the assertion that the claimed invention can be used to elicit an anti-HMFG immunological response in a mammal. In particular, Benvenuti, et al (*Gene Therapy* **7**: 605-611, 2000) teach that anti-idiotypic DNA vaccines, such as the vaccines disclosed in the specification, which comprises the polynucleotide sequences encoding a polypeptide comprising one or both of the immunoglobulin variable regions of monoclonal antibody 11D10, require the presence of both variable region genes for tumor protection. Consequently, one would not expect a mere fragment of a variable region of the monoclonal antibody to be capable of eliciting the same immunological response that the monoclonal antibody elicits in a mammal. Therefore, the asserted utility of the invention, which appears specific and substantial, is not credible.

The utility of the claimed invention is not well established. If the asserted utility is indicated to be nonspecific and insubstantial, because the claimed invention is not supported by a specific and substantial asserted utility, the credibility of the utility cannot be assessed.

Claim Rejections - 35 USC § 112

31. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

32. Claims 14 and 15 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention, because one skilled in the art could not make and/or use the claimed invention with a reasonable expectation of success without need to perform undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

As stated in the 35 USC § 101 rejection above, the specification fails to disclose sufficient guidance and direction to enable one skilled in the art to make and use the claimed invention. Moreover, there is no working exemplification of the use of the claimed invention to elicit an anti-HMFG immunological response in a mammal or to induce antitumor immunity in a mammal. In the absence of working exemplification commensurate in scope with the claims, one skilled in the art cannot predict whether the claimed invention can be used successfully to elicit an anti-HMFG immunological response in a mammal or to induce antitumor immunity in a mammal, because the art is

highly unpredictable. Nonetheless, based upon the state of the art, as evidenced by the teachings of Benvenuti, et al, one would not expect the claimed invention to be capable of eliciting an anti-HMFG immunological response. Although Benvenuti, et al teach that a polynucleotide encoding only the variable heavy chain of an anti-idiotypic antibody can elicit an immunological response in a mammal, Benvenuti, et al found that the polynucleotide is not capable of inducing protective antitumor immunity in a mammal. Based on the teachings of Benvenuti, et al, one skilled in the art would not be able to predict whether a polynucleotide encoding only the variable light chain of an anti-idiotypic antibody would be capable of eliciting an immunological response in a mammal, but it seems unlikely that the polynucleotide would be capable of inducing protective antitumor immunity in a mammal, since the polynucleotide encoding the heavy chain variable region of the antibody could not do so. Furthermore, it is even more unpredictable that a polynucleotide encoding only a small fragment of a variable heavy chain or the variable light chain of an anti-idiotypic antibody would be capable of eliciting an immunological response in a mammal, the polynucleotide is not capable of inducing protective antitumor immunity in a mammal. Thus, one skilled in the art could not make and/or use the claimed invention with a reasonable expectation of success without need to perform undue experimentation. Therefore, the specification fails to meet the enablement requirements of 35 USC § 112, first paragraph.

33. Claims 6-12, 16-19, 38, 41, 44, 45, 59-64, 66, 70, 71, and 76-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide comprising a polynucleotide sequence encoding both an immunoglobulin variable region containing the three light chain CDRs of antibody 11D10 and an immunoglobulin variable region containing the three heavy chain CDRs of antibody 1D10, wherein the variable regions are joined by a linker polypeptide of about 5 to about 20 amino acids, wherein said polynucleotides encode a polypeptide capable of eliciting an anti-HMFG immunological response in a mammal, a composition comprising said polynucleotide, a vector comprising said polynucleotide, a host cell comprising said vector, and a kit comprising said polynucleotide does not reasonably

provide enablement for a polynucleotide comprising a polynucleotide sequence encoding an immunoglobulin variable region containing the three light chain CDRs of antibody 11D10 or an immunoglobulin variable region containing the three heavy chain CDRs of antibody 1D10, or a polynucleotide comprising a polynucleotide sequence encoding both an immunoglobulin variable region containing the three light chain CDRs of antibody 11D10 and an immunoglobulin variable region containing the three heavy chain CDRs of antibody 1D10, wherein the variable regions are not joined by a linker polypeptide of about 5 to about 20 amino acids, or an immunogenic composition comprising said polynucleotide, or a composition comprising said polynucleotide and a pharmaceutically acceptable excipient, or a vector comprising said polynucleotide, or a host cell comprising said vector, or a kit comprising said polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a genus of polynucleotides, and vectors, host cells, compositions and kits comprising said polynucleotides, wherein said polynucleotides encode a polypeptide capable of eliciting an anti-HMFG immunological response in a mammal. However, the claims encompass polynucleotides, including polynucleotides that comprise a polynucleotide sequence encoding an immunoglobulin variable region containing the three light chain CDRs of antibody 11D10 *or* an immunoglobulin variable region containing the three heavy chain CDRs of antibody 11D10, which would not necessarily be expected to be capable of eliciting an anti-HMFG immunological response in a mammal. On the other hand, some of the claims, e.g., claim 64, encompass a polynucleotide comprising a polynucleotide sequence encoding *both* an immunoglobulin variable region containing the three light chain CDRs of antibody 11D10 and an immunoglobulin variable region containing the three heavy chain CDRs of antibody 11D10, wherein the variable regions are *or* are not joined by a linker polypeptide of about 5 to about 20 amino acids, which may or may not be expected to be capable of eliciting an anti-HMFG immunological response in a mammal.

While the specification teaches methods for making polynucleotides encoding polypeptides comprising the immunological variable domain of the light and heavy chains of monoclonal antibody 11D10, the specification does not teach methods, which are commensurate in scope with the claims, for making the claimed polynucleotides that encode polypeptides, *which are capable of eliciting an anti-HMFG immunological response in mammals*. In fact, the specification provides sufficient guidance, direction, and exemplification to use only one of the claimed species, namely a polynucleotide comprising a polynucleotide sequence encoding *both* an immunoglobulin variable region containing the three light chain CDRs of antibody 11D10 and an immunoglobulin variable region containing the three heavy chain CDRs of antibody 11D10, wherein the variable regions *are* joined by a linker polypeptide of about 5 to about 20 amino acids. Consequently, the teachings of the specification cannot be extrapolated to the enablement of the claimed invention and in the absence of a sufficiently enabling disclosure, one skilled in the art would not be able to make and/or use the claimed invention with a reasonable expectation of success without need to first perform undue experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. An analysis of the content of the specification and simultaneously weighing each of these factors indicates that one skilled in the art would not be able to make and/or use the claimed invention with a reasonable expectation of success without need to first perform undue experimentation and therefore the disclosure is insufficient to meet the enablement requirement of 35 USC §112, first paragraph.

The state of the art and the relative skill of those in the art is such that the production of chimeric antibodies, which comprise the light and heavy chain variable

domains of a murine monoclonal antibody and the light and heavy chain constant domains of a human antibody is routine and conventional, since the methodology required is well-established and because chimeric antibodies are generally less immunogenic than mouse antibodies, chimeric antibodies are more suitable for use in humans. Furthermore, it is rapidly becoming routine in the art to produce recombinant single chain antibodies comprising the variable domain of a monoclonal antibody's light chain joined by a polypeptide linker to the variable domain of a monoclonal antibody's heavy chain, where both the light and heavy chain variable domains contain the three complementarity-determining regions (CDRs) of those chains in approximately the same sequential and spatial arrangement as that in which they occur in the natural antibody. Moreover, it will become routine in the art to produce reshaped antibodies, e.g., humanized or Primatized™ antibodies, which are recombinant antibodies composed of light and heavy chain variable domains comprising the complementarity-determining regions (CDRs) of a murine monoclonal antibody but the framework or scaffolding regions of a human antibody; as the reshaped antibodies are generally even less immunogenic than chimeric antibodies, it will has become conventional to use reshaped antibodies as therapeutic agents in humans.

However, it is not routine or conventional in the art to make and use a polypeptide consisting of only a variable domain of either the light or the heavy chain of an antibody, because neither the light nor the heavy chain is inherently immunogenic of *a specific anti-paratope immune response*. Therefore, it is not routine or conventional in the art to make and use a polynucleotide than encodes such a polypeptide as an immunogen.

Despite recent advances in technology, antibody engineering is subject to a high degree of unpredictability, so that empirical determination is essential. Antibody structure is highly complex and very sensitive to even small alterations in amino acid sequence. The combination of the two variable regions of a light chain and a heavy chain defines the particular antigen-binding region or paratope of an antibody. An antibody binds an antigen by virtue of its ability to form a sterically and energetically favored molecular complex by a process that is dependent upon the complementary

alignment of a matrix of molecular determinants contained in the so-called "complementarity-determining regions" (CDRs) of the variable chains of the antibody with a matrix antigenic determinants contained by the antigen's epitope. Since the constant regions are not unique to an antibody, it is the conformation of the paratope of an antibody that defines its antigenicity, i.e., its idiotype. Immunizing a mammal with an antibody that specifically binds the epitope of the antigen produces an anti-idiotypic antibody. The paratope of an anti-idiotypic antibody mimics the complexities of the three-dimensional structure of an epitope present on an antigen to which the idiotypic antibody binds, because the anti-idiotypic antibody comprises a matrix of molecular determinants that are "recognized" or are complemented by the matrix of antigenic determinants contained by the idiotypic antibody's idiotype, which necessarily complement the antigenic determinants of the antigen's epitope. In the instant case, the specification teaches that an animal was immunized with monoclonal antibody BrE-1, which specifically binds an epitope of human milk fat globule (HMFG) protein, to produce the anti-idiotypic antibody, namely monoclonal antibody 11D10. The specification, then, teaches that immunizing an animal with monoclonal antibody 11D10 elicits the production of anti-anti-idiotypic antibodies in the animal that specifically bind the anti-idiotypic antibody's paratope, which mimics the epitope to which BrE-1 binds, and therefore immunizing the animal with monoclonal antibody 11D10 elicits the production of antibodies in the animal that specifically bind the epitope of HMFG to which the monoclonal antibody BrE-1 binds.

The specification does not provide working exemplification of the use of the claimed invention to elicit an anti-HMFG immunological response in a mammal. Nonetheless, in view of the exemplification of the use of monoclonal antibody 11D10 and upon consideration of the state of the art, it seems that the skilled artisan would have a reasonable expectation of successfully producing and using a polynucleotide comprising a sequence that encodes a single-chain antibody derived from the amino acid sequence of monoclonal antibody 11D10, comprising the variable regions of the light and heavy chains of the monoclonal antibody, because there is a reasonable expectation that the single-chain antibody would faithfully reproduce the paratope of the

monoclonal antibody. Alternatively, it seems that the skilled artisan would have a reasonable expectation of successfully producing an antibody that is able to elicit a specific anti-HMFG immunological response in a mammal, provided that polynucleotides encoding both the light and heavy chains of monoclonal antibody 11D10 are co-expressed in the same transfected cell, although the claims do not specifically encompass such an invention, because again the antibody that forms in the cell would be reasonably expected to faithfully reproduce the paratope of mouse monoclonal antibody 11D10. However, in view of the complexity of the antibody, the state of the art, and the amount of working exemplification disclosed in the specification, it also seems that the skilled artisan would not have a reasonable expectation of successfully producing and using the *claimed* invention, which includes a multitude of potentially non-working embodiments. For example, the skilled artisan would not have a reasonable expectation of successfully making and using a polynucleotide comprising a sequence that encodes only the variable region of either the light or the heavy chain of the monoclonal antibody, because based upon the structure of an antibody and the nature of its immunogenicity, as discussed in the paragraph above, it is highly unpredictable that the polypeptide encoded by such a polynucleotide would be capable of eliciting a specific anti-HMFG immunological response.

In fact, it appears that immunizing a mammal with a DNA molecule comprising a polynucleotide sequence encoding only one of the variable regions of an antibody cannot effectively elicit the desired immune response. Benvenuti, et al (*Gene Therapy* **7**: 605-611, 2000) and Benvenuti, et al (*Gene Therapy* **8**: 1555-1561, 2001) teach that a single-chain anti-idiotypic antibody comprising the variable regions of both the light and heavy chains of a parental antibody effectively elicits an immunological response in mammals, producing antibodies that are specifically reactive with the antigen to which the idiotype binds. Since it is difficult to demonstrate the absence of an immunological response in a mammal, Benvenuti, et al determined the reactivity of the immune sera produced in mammals immunized with the DNA encoding a single-chain antibody with a polypeptide comprising only one or the other variable region of either the light or heavy chain of the parental antibody. Benvenuti, et al (2001) found no immune reactivity with

polypeptides comprising only one or the other variable region of either the light or heavy chain of the parental antibody, which suggests that only antibodies that recognize determinants resulting from the combination of the variable regions of the light and heavy chains, but not present in the isolated variable regions are produced in response to anti-idiotypic immunization. Benvenuti, et al (2001) conclude, "[t]hese findings indicate that presentation of properly folded idiotypes results in a highly specific antibody response directed exclusively to private idiotypic determinants of the V_L/V_H combination of the immunogen" (abstract). Because the specific and desired immunogenicity of the anti-idiotypic antibody predominantly depends upon its precise quaternary structure, it seems evident that the conformation of a polypeptide comprising only a single variable domain of either the light or heavy chain of an antibody may not sufficiently resemble the conformation of the complex of the combined variable domains of both the light and heavy chains and might not faithfully reproduce the idiotype of the antibody to elicit a specific immune response, which would result in the production of antibodies or T-cells with the necessary specificity, avidity, and affinity to protect a mammal against a tumor bearing HMFG, which is an asserted utility of the claimed invention. In the absence of working exemplification, the skilled artisan would therefore not accept the assertion the claimed polynucleotides, those encompassed by the claim 6 in particular, encode a polypeptide that would be capable of eliciting an effective anti-HMFG immunological response. Moreover, the specification fails to provide sufficient guidance and direction to enable the skilled artisan to recognize which of the claimed species of polynucleotide might be capable or might not be capable of eliciting an anti-HMFG immunological response, which would be capable of protecting a mammal against a tumor.

Although Benvenuti, et al found that immunizing the animal with DNA encoding a polypeptide comprising only one or the other variable regions of the either the light or the heavy chain of the antibody resulted in the production of some antibodies, in the present case, the specification fails to teach that the variable regions of light and heavy chains of monoclonal antibody 11D10 are capable of eliciting any specific anti-HMFG immune response. Based upon the teachings of Benvenuti, et al, in the absence of

working exemplification that is reasonably commensurate in scope with the claims, the skilled artisan would not accept the assertion that the immune response elicited by immunizing a mammal with only one or the other of the variable regions of either the light or heavy chains of monoclonal antibody 11D10, would be sufficient to make the invention therapeutically useful. Furthermore, as discussed in the Office Action mailed May 17, 1999 (Paper No. 15), because of the sensitivity of the antibody's structure and function to amino acid substitutions, as evidenced by the teachings of Rudikoff, et al, Panka, et al, and Amit, et al, which were cited in Paper No. 15, again in the in the absence of working exemplification that is reasonably commensurate in scope with the claims, the skilled artisan would not accept the assertion an antibody or a polypeptide comprising one or both variable regions of the light or heavy chains of monoclonal antibody 11D10, in which the exact spatial and sequential arrangement of the CDRs of monoclonal antibody 11D10 is not faithfully reiterated, would be retain the specificity, affinity, or avidity of the monoclonal antibody, or that the immune response elicited by immunizing a mammal with a polynucleotide encoding such antibody or a polypeptide would be sufficient to make the invention therapeutically useful.

Although the conformation, i.e., three-dimensional structure of an antibody's antigen-binding region is highly sensitive to amino acid variation, as evidenced by the teachings of Rudikoff, et al, Panka, et al, and Amit, et al, provided that the recombinant antibody comprises both variable regions, it has become increasingly more routine to produce recombinant antibodies that retain the antigen-binding specificity and affinity of the natural antibody from the amino acid sequence of which the recombinants are derived. Accordingly, in view of the disclosure, one skilled in the art would be capable of making and using the invention of claim 64 with a reasonable expectation of success without having to perform undue experimentation, provided that the polynucleotide co-expresses polypeptides comprising the variable domains of the light and heavy chains of monoclonal antibody or a humanized version thereof in a single transfected cell, or alternatively, provided the polynucleotide expresses a fusion polypeptide comprising both variable domains of the light and heavy chains of the monoclonal antibody joined by a suitable linker, i.e., a single-chain antibody. However, for the reasons already

stated in the paragraphs above, one skilled in the art would not have a reasonable expectation of making and using the invention of claim 6, for example, without need to perform undue experimentation, because one skilled in the art could not predictably make and predictably use a polynucleotide encoding either a variable domain of the light chain or a variable domain of the heavy chain of monoclonal antibody 11D10, and not both, with a reasonable expectation of success, *where said polypeptide is capable of eliciting an anti-HMFG immunological response in a mammal.* Moreover, one skilled in the art could not predictably make and predictably use with a reasonable expectation of success, a polynucleotide encoding a variable domain of either the light chain or the heavy chain of monoclonal antibody 11D10 in which the amino acid sequence, spatial arrangement, or sequential sequence of the complementarity-determining regions have not been faithfully reproduced in the recombinant polypeptide encoded by the claimed polynucleotides, *where said recombinant polypeptide is capable of eliciting an anti-HMFG immunological response in a mammal.* As stated in the 35 USC § 101 rejection above, it is even more certain that the skilled artisan could not predictably make or predictably use with a reasonable expectation of success, a polynucleotide encoding only a portion of a variable domain of the either the light or heavy chains of monoclonal antibody 11D10 to produce an anti-HMFG immunological response in a mammal. Certainly a polynucleotide comprising only a single complementarity-determining region of either the light or heavy chains of monoclonal antibody 11D10 would not be expected to adopt a three-dimensional structure that would mimic the paratope of the monoclonal antibody and be capable of eliciting an anti-HMFG immunological response in a mammal.

Additionally, although practicing certain embodiments of the invention of claim 64 may not require undue experimentation, one skilled in the art could not predictably make and predictably use with a reasonable expectation of success, a polynucleotide comprising a sequence encoding a fusion polypeptide comprising both the variable domains of the light and heavy chains of monoclonal antibody, wherein said domains are *not* separated by a suitable linker polypeptide. It is well established in the art that a linker is an essential component of a single-chain antibody. While the length and

composition of the linker can significantly alter the yield and the biological activity of a single-chain antibody, there is sufficient guidance and direction in the art and the specification to enable the skilled artisan to determine the optimal length and composition of the linker of a single-chain antibody comprising the variable domains of the light and heavy chains of monoclonal antibody 11D10. However, one skilled in the art would not expect to be able to produce and use with a reasonable expectation of success, a single-chain antibody that does not comprise a suitable linker; and certainly in the absence of working exemplification and adequate guidance, undue experimentation would be required to do so.

In summary, the amount of exemplification, guidance, and direction in the specification is not reasonably commensurate in scope with the claims to enable the skilled artisan to make and use the claimed invention with a reasonable expectation of success without need to perform undue experimentation. Therefore, the disclosure fails to meet the enablement requirement of 35 USC § 112, first paragraph.

Amending claim 6 to delete the phrase "that is capable of eliciting an anti-HMFG immunological response in a mammal" can obviate the basis of this rejection. Alternatively, claim 6 could be amended so that it is drawn to a polynucleotide comprising a sequence or sequences that encode **both** an immunoglobulin variable domain of the light chain of monoclonal antibody 11D10 and an immunoglobulin variable domain of the heavy chain of monoclonal antibody 11D10, wherein said immunoglobulin variable regions comprise the three complementarity-determining regions of said domains *sequentially and spatially arranged in the manner in which they occur in monoclonal antibody 11D10*; such an amendment would also obviate the basis of this rejection. As a third alternative, claim 6 could be amended to recite, for example, the "[a] polynucleotide comprising a sequence encoding a polypeptide comprising the immunoglobulin variable domain of the light chain of monoclonal antibody 11D10 or a polypeptide comprising the immunoglobulin variable domain of the heavy chain of monoclonal antibody 11D10, where upon co-expression of said polypeptides in a mammalian cell, said polypeptides are capable of forming an antibody which is capable

of eliciting an anti-HMFG immunological response in a mammal. (Also see the 35 USC §112, second paragraph rejection below.)

However, Applicant is cautioned against the introduction of new matter.

34. Claims 6-19, 38, 41, 44, 45, 57-63, 66, 70, and 72-80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass a genus of nucleic acid molecules that comprise a polynucleotide sequence that encodes a polypeptide that comprises either the heavy chain variable domain or the light chain variable domain of the monoclonal antibody 11D10. Therefore, the claims encompass the genomic DNA molecule that encodes the light chain of monoclonal antibody 11D10 and the genomic DNA molecule that encodes the heavy chain of monoclonal antibody 11D10. Also, the claims encompass any allelic variants of the genes, which encode either the light or the heavy chain of the antibody, but which contain only silent polymorphisms, which do not cause alterations in the amino acid sequence of the 11D10 polypeptides. Furthermore, the claims encompass any alternatively spliced messenger RNA (mRNA) molecules and the cDNA molecules derived from such mRNA molecules, which encode either the heavy chain variable domain or the light chain variable domain of the monoclonal antibody 11D10.

However, despite the breadth of the claims, the written description only sets forth the structures of two species of the claimed genus, which encode the variable domains of the light and heavy chains of monoclonal antibody 11D10, respectively, namely SEQ ID NO: 1 and SEQ ID NO: 3. Therefore, the written description is not reasonably commensurate with the claims and therefore the specification would not reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (page 115).

Furthermore, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement that defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "[a]n adequate written description of a DNA [molecule] 'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Accordingly, the description of two species of the claimed genus, which are the polynucleotide sequences of cDNA molecules isolated from the hybridoma that produces monoclonal antibody 11D10, is not sufficient to enable one skilled in the art to recognize that Applicants had possession of the other members of the claimed genus. While it is not necessary to describe each and every member of a claimed genus, it is necessary to describe a representative number of the members of the claimed genus, but representative numbers of these members of the claimed genus have not been described in the specification and in the absence of adequate description, one skilled in the art cannot immediately envision the structures or features of each.

Furthermore, the isolated naturally occurring genomic DNA molecules (i.e., the gene and its allelic variants), which encode the polypeptide comprising the light and heavy chains of monoclonal antibody 11D10, would be expected to have introns and exons as well as regulatory elements. The structures of these genomic DNA molecules are not conventionally known in the art. Moreover, the specification fails to identify and

describe the structures of the 5'- and 3'- regulatory regions contained within the untranslated regions, the polynucleotide sequences of the introns, and the boundaries of the intron and exons that are essential to the function of the invention. In fact, the structures of naturally occurring genes with regulatory elements, untranslated regions, and introns and exons can only be determined empirically. Clearly, it is not possible to work backward from the known structure of a cDNA molecule to derive the unknown structure of the corresponding gene, which encodes the same polypeptide as the cDNA. See, for example, Harris et al, *Journal of the American Society of Nephrology*, **6**: 1125-1133, 1995; Ahn et al, *Nature Genetics,* **3**: 283-291, 1993; and Cawthon et al, *Genomics* 9: 446-460, 1991. Accordingly, in the absence of an adequate written description of a representative number of the species from within the claimed genus, the skilled artisan would not recognize from the disclosure that Applicant was in possession of the claimed genus of nucleic acids.

Furthermore, Applicant is reminded that conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

In summary, adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. With the exception of SEQ ID NO: 1 and SEQ ID NO: 3, the skilled artisan cannot immediately envision the detailed structure of the encompassed polynucleotides. Consequently, the disclosure is insufficient to meet the written description requirement of 35 USC 112, first paragraph and to support the generic claims in accordance with *The Guidelines for Examination of Patent Applications* (66 FR 1099-1111, 5 January 2001).

Amending claim 6 to recite, for example, the limitation "[a] polynucleotide comprising a sequence comprising SEQ ID NO: 1 or SEQ ID NO: 3, wherein said sequence encodes [...]" could obviate this rejection, because the amended claims would not encompass any polynucleotides that are not adequately described in the

specification to meet the written description requirement of 35 USC § 112, first paragraph.

35. Claims 6-12, 16-19, 38, 41, 44, 45, 59-71, and 76-80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 6 is drawn to a polynucleotide comprising a sequence encoding a polypeptide, wherein said polypeptide comprises an immunoglobulin variable region of antibody 11D10, wherein antibody 11D10 is produced by the hybridoma deposited under ATCC Accession No. HB-12020 *or progeny thereof.* The specification defines the term "progeny" of a hybridoma as "descendents of a hybridoma, which may or may not be completely identical to the original (parent) cell due to mutation or other adaptation, but that produce a monoclonal antibody that maintains the ability to escape immune tolerance, i.e., to cause an immune response against HMFG" (page 12, lines 15-18). However, the specification only describes a polynucleotide, which comprises a sequence encoding a polypeptide comprising an immunoglobulin variable region of antibody 11D10, which is produced by the hybridoma deposited under ATCC Accession No. HB-12020. Moreover, the specification does not adequately describe the claimed polynucleotides, which comprise a sequence encoding a polypeptide comprising an immunoglobulin variable region of antibody produced by the progeny of the hybridoma deposited under ATCC Accession No. HB-12020, which according to the specification may differ from the polynucleotide sequence encoding the antibody produced by the parental cell, namely 11D10. Although the claim requires the polynucleotides to encode a polypeptide that is capable of eliciting an anti-HMFG immune response, this does not adequately describe the members of the claimed genus of polynucleotides, but merely states what the polypeptide encoded by the claimed polynucleotides must be capable of doing.

The written description is not reasonably commensurate with the claims and would not therefore reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (page 115).

Furthermore, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement that defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "[a]n adequate written description of a DNA [molecule] 'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Accordingly, the description of a single species of the claimed genus is not representative of the claimed genus. Although the claims require the polynucleotide to encode a polypeptide having a particular biologic activity, one skilled in the art cannot envision the detailed structures of a representative number of members of the claimed genus. Furthermore, because the specification fails to describe a structural feature shared by each and every member of the claimed genus that might serve to enable one skilled in the art to recognize that, which is claimed, from that, which is not, the written description is not sufficient to enable one skilled in the art to recognize the members of

the claimed genus and to distinguish those members from the polynucleotides that are not claimed.

Furthermore, Applicant is reminded that conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

In summary, adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. With the exception of SEQ ID NO: 1 and SEQ ID NO: 3, the skilled artisan cannot immediately envision the detailed structure of the polynucleotides encompassed by the claims. Consequently, the disclosure is insufficient to meet the written description requirement of 35 USC 112, first paragraph and to support the generic claims in accordance with *The Guidelines for Examination of Patent Applications* (66 FR 1099-1111, 5 January 2001).

Amending claim 6 to delete the phrase "or progeny thereof" could obviate the basis of this rejection.

36. Claims 6-12, 16-19, 38, 41, 44, 45, 59-71, and 76-80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Presently claim 6 recites the limitation "that is capable of eliciting an anti-HMFG immunological response". However, there does not appear to be sufficient antecedent basis in the specification for recitation of this limitation in the claims. The specification discloses, for example, "the invention also includes polynucleotides comprising a sequence encoding a polypeptide having immunological activity of monoclonal anti-idiotype antibody 11D10" (page 4, lines 5 and 6), but it does not appear to disclose that

the polynucleotides of the invention encode polypeptides "capable of eliciting an anti-HMFG immunological response", as the claims read.

The Examiner notes that claim 6 was rejected under 35 USC § 112, second paragraph in the Office Action mailed May 17, 1999 (Paper No. 15), because the phrase "polypeptide having immunological activity of monoclonal anti-idiotype antibody 11D10" rendered the claim indefinite since it could not be ascertained to which immunological activity the claim refers. In response to the Office Action mailed May 17, 1999, Applicants amended claim 6 in Paper No. 6 to resolve the claim's evident lack of clarity and therefore the rejection of claim 6 under 35 USC § 112, second paragraph for the reason stated is withdrawn. Nevertheless, because the limitation does not appear to be adequately supported by the disclosure, the limitation appears to be new matter and recitation of the limitation in the claims therefore appears to violate the written description requirement of 35 USC § 112, first paragraph. Applicants are invited to point to particular disclosures in the specification that are believed to provide proper antecedent basis for recitation of the limitation in the claims. Otherwise, amending the claims to recite the explicit language of the specification could obviate the basis of this rejection.

37. The specification and claims 44, 45, and 79 are objected to and claims 57, 58, and 80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 44 recites the term "live virus". Although the term was recited in an originally filed claim, it does not appear that there is proper antecedent basis in the specification for recitation of this broad term in the claims. Therefore, the specification and claims 44, 45, and 79 are objected to as failing to meet the written description requirement of 35 USC § 112, first paragraph. It is noted, however, that the specification would provide adequate support for recitation of "live recombinant vaccinia virus" (see page 36, line 1). Again this matter could be resolved if Applicants are able to

point to particular disclosures in the specification, which are believed to properly support the broad subject matter of the present claims. Otherwise, Applicants could amend the specification to provide proper antecedent basis for recitation of the term "live virus" and obviate the basis of this objection. Appropriate action is required. See *In re Benno*, 768 F.2d 1340, 226 USPQ 683 (Federal Circuit 1985).

Currently claims 57 and 58 are drawn to a kit for detecting or quantitating a polynucleotide comprising a polynucleotide that *comprises a sequence* encoding a variable region of antibody 11D10 or a portion thereof. The amendment to claims 57 and 58 in Paper No. 26 effectively broadened the scope of the claims, since before the amendment the claims only encompassed a kit for detecting or quantitating a polynucleotide encoding a variable region of antibody 11D10 or a portion thereof, whereas now the claim encompasses a kit for detecting or quantitating a broader genus of polynucleotides, which must only comprise a polynucleotide sequence that encodes a variable region of the antibody or a portion thereof. However, there does not appear to be sufficient antecedent basis in the specification for recitation of the broader limitation in the claim and thus the amendment to claims 57 and 58 appears to violate the written description requirement of 35 USC § 112, first paragraph. Perhaps this matter could be resolved if Applicants are able to point to particular disclosures in the specification, which are believed to properly support the subject matter of the present claims. Otherwise, amending the claims to recite the explicit language of the specification could obviate the basis of this rejection.

38. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

39. Claims 6-12, 16-19, 38, 41, 44, 45, and 57-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-12, 16-19, 38, 41, 44, 45, 59-71, and 76-80 are vague and indefinite because claim 6 recites the term "capable of" in line 2. Recitation of the term renders

the claim vague and indefinite because it cannot be ascertained whether the claim requires the polypeptide encoded by the polynucleotide to be actually elicit an anti-HMFG immunological response in a mammal or alternatively, to merely have the potential of doing so. Moreover, the situation or circumstances in which the polypeptide is required to have the conditional ability of to elicit the anti-HMFG immunological response in the mammal are not defined by the claims. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending claims 6 to delete the phrase "that is capable of eliciting an anti-HMFG immunological response in a mammal" can obviate this rejection. Alternatively, amending the claim to recite the situation or conditions wherein or whereby said polypeptide would be capable of eliciting an anti-HMFG immunological response can obviate this rejection.

Claims 9, 10, and 78 are indefinite because the claims recite the limitation "wherein the immunoglobulin variable region is contained in" SEQ ID NO: 2 or SEQ ID NO: 4, respectively. The claims lack clarity because it is not clear whether the immunoglobulin variable region to which claims 9 and 10 refer is the immunoglobulin variable region containing the three light chain complementarity determining regions or the immunoglobulin variable region containing the three heavy chain complementarity determining regions, according to claim 6, from which claims 9 and 10 depend. Amending claim 9 to recite "light chain" before "variable" and amending claim 10 to recite "heavy chain" before "variable" can obviate this rejection. Alternatively, amending claims 9 and 10 to recite, for example, "[a] polynucleotide according to claim 6, wherein said polynucleotide encodes a polypeptide that comprises the polynucleotide sequence set forth in SEQ ID NO: 2" could obviate this rejection. However, as with any amendment, Applicants are cautioned against the introduction of new matter.

Claims 11, 12, and 78 are indefinite because the claims recite the limitation "wherein the encoding sequence is contained in the variable region encoding sequence in" SEQ ID NO: 1 or SEQ ID NO: 3, respectively. Recitation of the limitation in the claims renders the claims indefinite because it is unclear to which or what "variable region encoding sequence" in SEQ ID NO: 1 or SEQ ID NO: 3 the claims refer.

Furthermore, although the claims require the encoding sequence of claim 6 to be *contained in* the variable region encoding sequence in SEQ ID NO: 1 or SEQ ID NO: 3, it seems apparent that the encoding sequence of claim 6 would necessarily comprise the entire variable region encoding sequence to encode an immunoglobulin variable region of an antibody. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending claims 11 and 12 to recite, for example, "[a] polynucleotide according to claim 6, wherein said polynucleotide comprises the polynucleotide sequence set forth in SEQ ID NO: 1" could obviate this rejection.

Claims 41, 44, 45, 61, 66, and 79 are indefinite because claim 41 recites the limitation "[an] immunogenic composition comprising the polynucleotide of claim 6". Recitation of the limitation renders the claim indefinite, because in light of the disclosure, it appears that the invention provides a polynucleotide that encodes a polypeptide that is immunogenic, not a polynucleotide that is immunogenic. In fact, it would seem that it would be undesirable to have an immunogenic composition comprising a polynucleotide encoding an immunogenic polypeptide, when the immune response that is sought is an immune response to the polypeptide and not to the polynucleotide. It is also noted that double-stranded DNA is not generally immunogenic in mammals, although the claims are not limited to double-stranded DNA molecules. Nevertheless, if the polynucleotide of claim 6 were double-stranded, the immunogenicity of the claimed composition would likely depend upon the immunogenic nature of the other undisclosed components of the composition. Consequently, it is unclear whether the claims distinctly set forth the subject matter that Applicants regard as the invention. In view of the lack of clarity, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 44 and 45 are indefinite because claim 44 recites the terms "live virus" and "viral expression vector". Recitation of the term renders the claim indefinite because it is unclear whether the term encompasses expression vectors that merely comprise viral components, e.g., the Rous sarcoma virus (RSV) promoter, or only expression vectors comprising a provirus, i.e., a plasmid capable of producing functional

virus after transfection into a supportive host cell. Also, it appears that the specification provides only one example of the latter type of vector that could possibly be used to elicit an immunological response in a mammal, namely a vaccinia virus (pages 34-36). Otherwise, the specification also provides the example of baculovirus, but baculovirus only infects insect cells. Additionally, it is noted that the specification uses the term "bacterial viruses" (page 34, line 35), which is an uncommon term in the art, as generally the term "bacteriophages" is used to avoid confusing the "bacteriophages" with "viruses" that infects eukaryotic cells. Therefore, because claim 44 recites the term "live virus" and "viral expression vector", it is noted that in view of the uncommon use of the term "viruses" in the specification and the uncertainty of the meaning encompassed by the term "viral expression vector", one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 59, 77, and 78 are indefinite because claim 59 recites the limitation "wherein antibody 11D10 has the light and heavy chain variable region sequences contained in SEQ ID NO: 2 and SEQ ID NO: 4, respectively". Recitation of the limitation renders the claim indefinite because it is unclear to which light and heavy chain variable region sequences contained in SEQ ID NO: 2 or SEQ ID NO: 4 the claim refers. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending claim 59 to recite, for example, the limitation "wherein antibody 11D10 has the light and heavy chain variable region encoding sequences of SEQ ID NO: 2 and SEQ ID NO: 4, respectively" can obviate this rejection.

Claims 57, 58, and 80 are indefinite because claims 57 and 58 recite "a kit for detection or quantitation of a polynucleotide comprising a polynucleotide which comprises a sequence encoding a variable region of antibody 11D10 or a portion thereof, said kit comprising **the polynucleotide**" (emphasis added) of claim 14, or 15, respectively. Recitation of the phrase renders the claim indefinite because it cannot be ascertained whether the polynucleotide (emphasized) refers to the polynucleotide of line 1 or the polynucleotide of line 2 of the claims. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 57, 58, 70, and 80 are vague and indefinite because claims 57, 58, and 70 recite the term "suitable packaging". The term "suitable" is a relative term, which is not defined by the claims. Recitation of the term renders the claims vague and indefinite because it cannot be determined to what purpose and extent the claims require the packaging to be suitable. Moreover, the specification does not provide a standard for ascertaining the requisite degree of suitability required of the packaging by the claims. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending claims 57 and 58 to delete "suitable" can obviate this rejection.

Claims 60, 61, and 79 are indefinite because claims 60 and 61 recite the limitation "further comprising an amount of polynucleotide sufficient to elicit an anti-HMFG immunological response". Recitation of the limitation renders the claims indefinite because according to claims 38 and 41, from which claims 60 and 61 respectively depend, the composition already comprises at least an amount of the polypeptide of claim 6 and so it not clear that the compositions of claims 60 and 61 can actually *further* comprise an amount of the polynucleotide. Nevertheless, if claims 60 and 61 further comprise an amount of polynucleotide sufficient to elicit an anti-HMFG immunological response, then presumably the compositions of claims 38 and 41 do not comprise a sufficient amount of the polynucleotide to elicit an anti-HMFG immunological response. Finally, it is not clear whether the amount of the polynucleotide contained in the compositions of claims 60 and 61 is an amount sufficient to elicit an immunological response in a mammal or perhaps, in cell culture or elsewhere. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 64, 65, 71, and 76-79 are indefinite because claim 64 recites the phrase "an immunoglobulin variable region containing the three light chain CDRs of antibody 11D10 and an immunoglobulin variable region containing the three heavy chain CDRs of antibody 11D10". Recitation of the phrase in the claims renders the claims indefinite because it is unclear whether the claim is intended to encompass a polynucleotide encoding both an immunoglobulin variable region containing the three light chain CDRs

in any order and an immunoglobulin variable region containing the three heavy chain CDRs in any order, or only in the order in which the CDRs occur in the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 65, 76, 78, and 79 are indefinite because claim 65 recites the term "linked polypeptide". The term generally used in the art is "linker" and unless the term "linked polypeptide" is defined in the specification, because of the use of an irregular term to refer to a linker, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. If Applicants are able to point to specific disclosures in the specification, which define the term "linked polypeptide", this rejection might be obviated; otherwise, amending the claim to recite "linker" before "polypeptide" can obviate this rejection.

Claims 72-75 are indefinite because claims 72 and 73 recite the phrase "an immunoglobulin variable region containing the three light [*or* heavy] chain CDRs in" SEQ ID NO: 2 or SEQ ID NO: 4, respectively. Recitation of the phrase in the claims renders the claims indefinite because it is unclear whether the claim is intended to encompass a polynucleotide encoding an immunoglobulin variable region containing the three light or heavy chain CDRs in any order, or only in the order in which the CDRs occur in the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 76-80 are indefinite because the claims recite the phrase "any of claims". The claims lack clarity, rendering the claims indefinite, because it is unclear whether the claims refer to only one of any of the claims listed or more than one of any of the claims. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending claims 76-80 to insert "one" after "any" can obviate this rejection.

40. Claims 14, 15, and 72-75 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention.

Evidence that claims 14, 15, and 72-75 fail to correspond in scope with that which Applicants regard as the invention can be found in Paper No. 26 filed December 4, 2001. In that paper, Applicants have stated, "[the 35 USC § 101] rejection is due to an erroneous assumption by the Office that the claimed polynucleotides are naturally-occurring" and "the polynucleotide sequences of the invention are not naturally-occurring in the sense that they arose due to manipulations to make an antibody-producing hybridoma, which does not occur in nature" (page 14, paragraph 5). These statements indicate that the invention is different from what is defined in the claims because the claims encompass naturally occurring products produced by the hybridoma that produces the monoclonal antibody 11D10 and also the lymphocyte from which the hybridoma had to have been derived, which also produces the monoclonal antibody 11D10. As the claims are written, the subject matter of the claims cannot be distinguished from such naturally occurring products and therefore it is evident that that claims 14, 15, and 72-75 fail to correspond in scope with that which Applicants regard as the invention.

Claim Rejections - 35 USC § 102

41. Claims 6-12, 14, 15, 38, 41, 57-63, 70, and 72-80 are rejected under 35 U.S.C. 102(a) as being anticipated by Chakraborty, et al (*Journal of Immunotherapy* **18**: 95-103, 1995).

Chakraborty, et al teach monoclonal antibody 11D10, which is produced by a hybridoma. The polynucleotides encoding the light and heavy chains of monoclonal antibody 11D10 are inherent features of the hybridoma. Because the subject matter of the claims cannot be distinguished from the polynucleotides of which the hybridoma is composed, the teachings of Chakraborty, et al anticipate the claimed invention. All the limitations of the claims are met.

Amending claims 6, 72, and 73 to recite, for example, the term "isolated", "purified", or "recombinant" before "polynucleotide" can obviate this rejection, because the recitation of such a limitation would serve to distinguish the subject matter of the claims from the products of the prior art.

Claim Rejections - 35 USC § 103

42. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

43. Claims 6-12, 14-19, 38, 41, 44, 45, 57-66, and 70-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhattacharya-Chatterjee, et al (In *Antigen and Antibody Molecular Engineering in Breast Cancer Diagnosis and Treatment,* Ceriani, RL, Ed., Plenum Press: New York, pp. 139-148, 1994) in view of Chakraborty, et al (*Proceedings of the American Association for Cancer Research* **35**: 497, Abstract No. 2963) and in further view of Kennedy, et al (*Biotechniques* **3**: 404-410, 1985) and WO 94/11508-A2 (26 May 1994) or Spooner, et al (*Gene Therapy* **2**: 173-180, 1995) and Stevenson, et al (*Immunological Reviews* **145**: 211-228, 1995) and in still further view of Herlyn, et al (*Hybridoma* **14**: 159-166, 1995).

Bhattacharya-Chatterjee, et al teach a murine anti-idiotypic monoclonal antibody 11D10, which can be produced by immunizing a mammal with a monoclonal antibody that specifically binds human milk fat globule (HMFG) protein, namely BrE-1, and isolating a hybridoma that expresses the polynucleotide sequences encoding the light and heavy chains of a monoclonal antibody that binds specifically to the paratope of the monoclonal antibody BrE-1 (pages 140 and 141). Bhattacharya-Chatterjee, et al teach that the monoclonal antibody 11D10 elicits an anti-HMFG immunological response in mammals, namely mice and rabbits immunized with the antibody (page 142). Bhattacharya-Chatterjee, et al teach that patients diagnosed with breast cancer have Id matching sera, which suggests that the antibody may be specially suitable as a potential candidate agent for active anti-Id immunotherapy (page 144).

However, Bhattacharya-Chatterjee, et al do not teach that the murine anti-idiotypic monoclonal antibody 11D10 can be used as an immunogen to immunize a

mammal to induce antitumor immunity in the immunized mammal by activating both humoral and cellular immune anti-HMFG immunological response in the mammal.

Nonetheless, Chakraborty, et al teach that anti-HMFG, Id-specific humoral and cellular immunological responses can be elicited in monkeys by immunizing the monkeys with monoclonal antibody 11D10. Chakraborty, et al conclude, "[t]hese results indicate that alum precipitated anti-Id 11D10 can induce breast cancer specific antibodies in non-human primates and can serve as a network antigen for breast cancer patients" (abstract).

Therefore, in view of the teachings of Chakraborty, et al it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that the murine monoclonal antibody 11D10 of Bhattacharya-Chatterjee, et al, when used to immunize mammals having primed anti-HMFG B- and/or T-cells, is capable of inducing antitumor immunity in the immunized mammal by activating the primed B- and T-cells of the mammal and thereby eliciting an anti-HMFG immunological response in the mammal, because Chakraborty, et al concluded that the antibody can induce breast cancer specific antibodies in mammals and can serve as a breast network antigen in patients diagnosed with breast cancer. One of ordinary skill in the art would have been motivated at the time the invention was made to use the murine monoclonal antibody 11D10 of Bhattacharya-Chatterjee, et al to immunize mammals having primed anti-HMFG B- and T-cells, because upon immunizing the mammal with the monoclonal antibody, the monoclonal antibody is capable of inducing antitumor immunity in the immunized mammal by activating the primed B- and T-cells of the mammal and thereby eliciting an anti-HMFG immunological response in the mammal and there had been a long-felt need to develop more efficacious methods for treating patients diagnosed with breast cancer.

However, neither Bhattacharya-Chatterjee, et al nor Chakraborty, et al teach an immunogenic composition comprising polynucleotides that comprise a polynucleotide sequence that would encode a polypeptide that elicits an anti-HMFG immunological response in a mammal, wherein said polypeptide comprises the light chain and/or the heavy chain of monoclonal antibody 11D10. Furthermore, neither Bhattacharya-

Chatterjee, et al nor Chakraborty, et al teach that the immunogenic composition, which could be used to immunize a mammal, should be sterile or that the polynucleotide sequence encoding the antibody's light and/or heavy chains could be cloned into either a cloning or expression vector, which could be transfected into host cells. Also, Bhattacharya-Chatterjee, et al and Chakraborty, et al do not disclose a kit comprising such an anti-HMFG immunological composition. Finally, neither Bhattacharya-Chatterjee, et al nor Chakraborty, et al teach that a fragment of the polynucleotide encoding the variable light or variable heavy chains of monoclonal antibody could be used as a probe to detect the presence of the polynucleotide sequence in host cells, for example, or disclose that such probes could be contained in a kit.

Nevertheless, Kennedy, et al teach that anti-idiotypic (anti-Id) immunization may offer a number of advantages and because anti-Id could be produced that mimic tumor antigens, an anti-Id vaccine might be capable of eliciting antitumor immunity in patients (page 408, column 1). Kennedy, et al teach that such anti-Id vaccines may be advantageous, because the anti-Id vaccine would induce immunity against a single epitope present on the tumors and bypass the risk of producing a deleterious autoimmune response against the host, which might occur if a vaccine is composed of a protein, attenuated virus, or killed cell, which shares antigenic determinants with the host. However, Kennedy, et al also teach that anti-Id immunization has a potential disadvantage, namely the need to repeatedly immunize the host to boost the immunological response, which can be dangerous since repeated immunizations may trigger anaphylaxis, i.e., a severe and sometimes fatal adverse immune reaction, in the immunized animal (page 408, column 2). On the other hand, Kennedy, et al teach, "methods are becoming available to produce chimeric antibody molecules in which the V region is of mouse origin and the rest of the molecule is human in nature" (page 408, column 2). Kennedy, et al teach that the production of such chimeric antibodies would be advantageous because such chimeric antibodies could be administered to patients, thereby lessening the potential for producing anaphylaxis as a result of multiple injections of an anti-Id vaccine preparation (page 408, column 2).

Additionally, WO 94/11508-A2 teaches methods for producing anti-idiotypic chimeric antibodies that bind specifically to the paratope of anti-HMFG antibodies (pages 33 and 34, Example 12; pages 42 and 43, Example 29). Furthermore, WO 94/11508-A2 teaches that such anti-idiotypic antibodies are suitable for immunizing humans against neoplasias, i.e., cancer (page 1) and teaches methods for treating humans with immunogenic compositions comprising the chimeric antibodies (claim 54, for example). WO 94/11508-A2 also teach methods for making and using cloning and expression vectors, which comprise polynucleotide sequences encoding the light and heavy chains of the antibodies, and methods for making and using host cells comprising such cloning or expression vectors (claims 31 and 40, for example). WO 94/11508-A2 teaches kits that can comprise antitumor vaccines in sterile containers (claim 49, for example).

Furthermore, Spooner, et al teach that DNA vaccination with an composition comprising polynucleotide sequence encoding surrogate antigens, such as anti-idiotype antibodies, may be a means for breaking immunological tolerance and lead to the generation of tumor-specific immune response (abstract; page 177, Table 2). Spooner, et al teach that DNA vaccination may offer the substantial advantage of inducing both humoral, i.e., antibody, and cellular, i.e., T cell, immune response to an antigen (page 173, column 2). Spooner, et al disclose that vaccination with polynucleotides encoding antigens can produce antitumor immunological activity in an animal (page 179, column 1).

Stevenson, et al also teach that anti-idiotypic vaccines can induce activation of both arms of the immune system (page 218). Stevenson, et al disclose that initial studies have yielded encouraging results, which suggest that DNA vaccination with polynucleotide sequences encoding anti-idiotypic antibodies can elicit the production of tumor-reactive antibodies *in vivo* (page 219). Stevenson, et al teach that expression vectors comprising viral transcription regulatory elements, which express chimeric anti-idiotypic antibodies, can be formulated as a composition suitable for injection into animals (page 219, Figure 3). Also, Stevenson, et al disclose that multiple

immunizations of animal with DNA vaccine can be made without inducing an adverse immune reaction since double-stranded DNA is not highly immunogenic.

Therefore, in further view of the teachings of Bhattacharya, et al and WO 94/11508-A2, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to isolate and clone the cDNA molecules encoding the light and heavy chain variable regions of the mouse monoclonal antibody 11D10 of Bhattacharya-Chatterjee, et al and Chakraborty, et al from the hybridoma that produces the antibody and to use the cloned cDNA molecules to construct an expression vector that expresses a messenger RNA (mRNA) molecule encoding a single chain chimeric antibody that has the same binding specificity as monoclonal antibody 11D10, because Bhattacharya, et al and WO 94/11508-A2 teach that such a vector can be used to produce sufficient quantities of the antibody to formulate a vaccine composition that can be used to immunize an animal against a tumor. One of ordinary skill in the art at the time the invention was made would have been motivated to produce such an expression vector to produce a quantity of the antibody sufficient to immunize a mammal against a tumor.

Alternatively, in further view of the teachings of Spooner, et al and Stevenson, et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to isolate and clone the cDNA molecules encoding the light and heavy chain variable regions of the mouse monoclonal antibody 11D10 of Bhattacharya-Chatterjee, et al and Chakraborty, et al from the hybridoma that produces the antibody and to use the cloned cDNA molecules to construct an expression vector that expresses a messenger RNA (mRNA) molecule encoding a single chain chimeric antibody that has the same binding specificity as monoclonal antibody 11D10, because Spooner, et al and Stevenson, et al teach plasmid DNA encoding anti-idiotypic chimeric antibodies can be used to immunize a mammal against a tumor. One of ordinary skill in the art at the time the invention was made would have been motivated to produce such a DNA vaccine, because Spooner, et al and Stevenson, et al teach that the use of a DNA vaccine can be advantageous, overcoming some of the limitations of using the anti-idiotypic antibody as a vaccine, since the mammal can be safely immunized

multiple times and induce the activation the humoral and cellular arms of the immune system.

However, Bhattacharya-Chatterjee, et al, Chakraborty, et al, Spooner, et al, and Stevenson, et al do not teach that the expression vector can be vaccinia or that recombinant vaccinia comprising polynucleotide sequences that encode an anti-idiotypic antibody can be used to immunize mammals and elicit an anti-HMFG immune response in the mammals.

Herlyn, et al, on the other hand, teach that recombinant vaccinia viruses comprising polynucleotide sequences encoding anti-idotypic antibodies can be used to immunize mammals. Moreover, Herlyn, et al teach that recombinant vaccinia viruses expressing anti-idiotypic antibodies can elicit a more robust immunological response in the mammals than immunization with anti-idiotypic antibodies, producing higher antibody titers in the mammals.

Therefore, in further view of the teachings of Herlyn, et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to isolate and clone the cDNA molecules encoding the light and heavy chain variable regions of the mouse monoclonal antibody 11D10 of Bhattacharya-Chatterjee, et al and Chakraborty, et al from the hybridoma that produces the antibody and to use the cloned cDNA molecules to construct an vaccinia expression vector that expresses a messenger RNA (mRNA) molecule encoding a single chain chimeric antibody that has the same binding specificity as monoclonal antibody 11D10, because Herlyn, et al teach that anti-idiotypic antibody-expressing recombinant vaccinia virus can be used to achieve higher antibody titers in immunized animals than anti-idiotypic antibody vaccination alone. One of ordinary skill in the art at the time the invention was made would have been motivated to produce and use a recombinant vaccinia virus that expresses an 11D10-derived single-chain antibody because it is desirable to elicit as robust an immune response as possible and Herlyn, et al teach that a more robust immune response can be elicited by recombinant vaccinia virus expressing anti-idiotypic antibodies.

Although none of the cited references explicitly teach that the nucleic acid molecules encoding the light or heavy chain variable regions of monoclonal antibody can be used as probes to detect the presence of the polynucleotide sequences encoding the antibody in host cells, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use portions of the cloned cDNA molecules encoding the light and heavy chain variable domains of monoclonal antibody 11D10 as a probes to detect the presence of nucleotide sequences encoding the antibody in host cells, because such methods are conventional and routine. One of ordinary skill in the art at the time the invention was made would have been motivated to manufacture a kit comprising suitable probes comprising polynucleotide sequences encoding a portion of the variable regions of monoclonal antibody 11D10, because kits provide greater ease to practicing a method and are convenient.

44. Claims 6-12, 14-19, 38, 41, 44, 45, 57-66, and 70-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakraborty, et al (*Cancer Research* **55**: 1525-1530, 1995) in view of Spooner, et al (*Gene Therapy* **2**: 173-180, 1995) and Stevenson, et al (*Immunological Reviews* **145**: 211-228, 1995) or Kennedy, et al (*Biotechniques* **3**: 404-410, 1985) and WO 94/11508-A2 (26 May 1994) and in further view of Herlyn, et al (*Hybridoma* **14**: 159-166, 1995).

Chakraborty, et al teach immunization of monkeys with murine monoclonal antibody 11D10 induces antitumor immunity in the animals (abstract). Chakraborty, et al disclose, "[a]ll monkeys developed high titers of antibodies against the immunizing mouse immunoglobulin [...] which reacted with breast cancer cell lines" (abstract). The antibodies produced in the monkeys reacted bound specifically to human milk fat globule (HMFG) protein (abstract). Chakraborty, et al also teach that immunization of mice and rabbits with the monoclonal antibody also induced antitumor immunity in those animals, suggesting that the antibody is capable of inducing immune responses across species barriers (abstract), thus Chakraborty, et al teach that the antibody elicits an anti-HMFG immunological response in mammals. Furthermore, Chakraborty, et al teach that the immunized monkeys developed cellular immune responses as demonstrated by

T-cell proliferation assays (abstract). Chakraborty, et al teach that the same adjuvant and dose of the monoclonal antibody, which will be used in clinical trials, was used to immunize the monkeys (page 1525, column 2). Chakraborty, et al teach that the final immunogenic composition, which was used to immunize the monkeys, was prepared aseptically and was therefore sterile (page 1526, column 1). Chakraborty, et al conclude, "[t]hese studies, therefore, are likely to predict the safety and efficacy of this anti-Id to induce antitumor antibodies in breast cancer patients" (page 1525, column 2).

However, Chakraborty, et al do not teach an immunogenic composition comprising polynucleotides that comprise a polynucleotide sequence that would encode a polypeptide that elicits an anti-HMFG immunological response in a mammal, wherein said polypeptide comprises the light chain and/or the heavy chain of monoclonal antibody 11D10. Furthermore, Chakraborty, et al do not teach that the immunogenic composition, which could be used to immunize a mammal, should be sterile or that the polynucleotide sequence encoding the antibody's light and/or heavy chains could be cloned into either a cloning or expression vector, namely a vaccinia virus expression vector, which could be transfected into host cells. Also, Chakraborty, et al do not disclose a kit comprising such an anti-HMFG immunological composition. Finally, Chakraborty, et al do not teach that a fragment of the polynucleotide encoding the variable light or variable heavy chains of monoclonal antibody could be used as a probe to detect the presence of the polynucleotide sequence in host cells, for example, or disclose that such probes could be contained in a kit.

Kennedy, et al, WO 94/11508-A2, Spooner, et al, and Stevenson, et al teach that which is set forth in the 35 USC § 103(a) rejection above.

Therefore, in view of the teachings of Kennedy, et al and WO 94/11508-A2, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to isolate and clone the cDNA molecules encoding the light and heavy chain variable regions of the mouse monoclonal antibody 11D10 of Chakraborty, et al from the hybridoma that produces the antibody and to use the cloned cDNA molecules to construct an expression vector that expresses a messenger RNA (mRNA) molecule encoding a single chain chimeric antibody that has the same binding

specificity as monoclonal antibody 11D10, because Kennedy, et al and WO 94/11508-A2 teach that such a vector can be used to produce sufficient quantities of the antibody to formulate a vaccine composition that can be used to immunize an animal against a tumor. One of ordinary skill in the art at the time the invention was made would have been motivated to produce such an expression vector to produce a quantity of the antibody sufficient to immunize a mammal against a tumor.

Alternatively, in view of the teachings of Spooner, et al and Stevenson, et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to isolate and clone the cDNA molecules encoding the light and heavy chain variable regions of the mouse monoclonal antibody 11D10 of Chakraborty, et al from the hybridoma that produces the antibody and to use the cloned cDNA molecules to construct an expression vector that expresses a messenger RNA (mRNA) molecule encoding a single chain chimeric antibody that has the same binding specificity as monoclonal antibody 11D10, because Spooner, et al and Stevenson, et al teach plasmid DNA encoding anti-idiotypic chimeric antibodies can be used to immunize a mammal against a tumor. One of ordinary skill in the art at the time the invention was made would have been motivated to produce such a DNA vaccine, because Spooner, et al and Stevenson, et al teach that the use of a DNA vaccine can be advantageous, overcoming some of the limitations of using the anti-idiotypic antibody as a vaccine, since the mammal can be safely immunized multiple times and induce the activation the humoral and cellular arms of the immune system.

However, Chakraborty, et al, Spooner, et al or Stevenson, et al do not teach that the expression vector can be vaccinia or that recombinant vaccinia comprising polynucleotide sequences that encode an anti-idiotypic antibody can be used to immunize mammals and elicit an anti-HMFG immune response in the mammals.

Herlyn, et al, on the other hand, teach that recombinant vaccinia viruses comprising polynucleotide sequences encoding anti-idotypic antibodies can be used to immunize mammals. Moreover, Herlyn, et al teach that recombinant vaccinia viruses expressing anti-idiotypic antibodies can elicit a more robust immunological response in

the mammals than immunization with anti-idiotypic antibodies, producing higher antibody titers in the mammals.

Therefore, in further view of the teachings of Herlyn, et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to isolate and clone the cDNA molecules encoding the light and heavy chain variable regions of the mouse monoclonal antibody 11D10 of Chakraborty, et al from the hybridoma that produces the antibody and to use the cloned cDNA molecules to construct an vaccinia expression vector that expresses a messenger RNA (mRNA) molecule encoding a single chain chimeric antibody that has the same binding specificity as monoclonal antibody 11D10, because Herlyn, et al teach that anti-idiotypic antibody-expressing recombinant vaccinia virus can be used to achieve higher antibody titers in immunized animals than anti-idiotypic antibody vaccination alone. One of ordinary skill in the art at the time the invention was made would have been motivated to produce and use a recombinant vaccinia virus that expresses an 11D10-derived single-chain antibody because it is desirable to elicit as robust an immune response as possible and Herlyn, et al teach that a more robust immune response can be elicited by recombinant vaccinia virus expressing anti-idiotypic antibodies.

Although none of the cited references explicitly teach that the nucleic acid molecules encoding the light or heavy chain variable regions of monoclonal antibody can be used as probes to detect the presence of the polynucleotide sequences encoding the antibody in host cells, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use portions of the cloned cDNA molecules encoding the light and heavy chain variable domains of monoclonal antibody 11D10 as a probes to detect the presence of nucleotide sequences encoding the antibody in host cells, because such methods are conventional and routine. One of ordinary skill in the art at the time the invention was made would have been motivated to manufacture a kit comprising suitable probes comprising polynucleotide sequences encoding a portion of the variable regions of monoclonal antibody 11D10, because kits provide greater ease to practicing a method and are convenient.

In traversing the rejection of the claims under 35 USC § 102(b), which was made in the Office Action mailed May 17, 1999 and maintained in the Office Action mailed April 24, 2001, Applicants' remarked that Chakraborty, et al (*Cancer Research* **55**: 1525-1530, 1995) is an improper 35 USC § 102(b) reference. While it is true that Chakraborty, et al is not available as prior art under 35 USC § 102(b), the reference is available as prior art under 35 USC §102(a); therefore, this rejection under 35 USC § 103(a) is proper.

Applicants further traversed the rejection arguing that the cited references failed to provide enabling disclosure of the claimed invention, while noting "the Examiner alleges that there is evidence to the contrary in the form of the publication policy of Cancer Research, requiring authors to make freely available biological materials that were used in the research reported" (page 12, paragraph 1). Although it is noted that Applicants' representative stated her awareness of the publication policy of the journal *Cancer Research* in Paper No. 19 (page 8), Applicants remarked later in Paper No. 26, "the publication policy of Cancer Research did not serve to place the 11D10 hybridoma into the hands of the public by virtue of Applicants publishing their research in this journal" (page 13, paragraph 3). "Applicants respectfully submit that the journal merely has a policy that authors agree to make freely available to others materials used in reported research, but does not require that the authors do so."

In response to Applicants' argument, the reference cited as a basis of rejection under 35 USC § 102(a) was published in the April 1 issue of 1995. The journal of *Cancer Research* publishes Instructions for Authors in the first issue of the year, so therefore the Instructions for Authors, which appeared in the January 1 issue of 1995, were applicable at the time the authors of the prior art reference published a report of their research. The Instructions for Authors includes the journal's Policy Concerning Availability of Materials (page 207, column 1), which states:

> It is understood that by publishing any work in *Cancer Research* the authors agree to make freely available to other academic researchers any cells, clones of cells or DNA or antibodies, etc. that were used in the research reported and that are not available from commercial suppliers.

In view of the journal's Policy Concerning Availability of Materials it appears that by publishing any work in the journal, which the authors of the cited prior art reference did, the authors acknowledged and accepted the policy, agreeing to make freely available to other academic researchers any cells, clones of cells, or antibodies that were used in the research reported. Because the cited prior art reference published in Cancer Research discloses the use of monoclonal antibody 11D10 and the hybridoma that produces the monoclonal antibody, it appears that the monoclonal antibody and the hybridoma were attainable, upon request, by any academic researcher, provided that the authors were willing and able to comply with the acknowledged and accepted policy of the journal. Consequently, contrary to Applicants' assertions, monoclonal antibody 11D10 and the hybridoma that produces the antibody should have been attainable upon request by another party.

For the reasons stated above, the declarations filed under 37 CFR §1.132 by the co-inventors stating that neither monoclonal antibody nor the hybridoma that produces the monoclonal antibody were distributed to any person other than those individuals whom were working under the direct supervision of the co-inventors are deficient. The fact that Applicants' did not distribute the antibody or the hybridoma to any other person does not constitute evidence that the antibody and the hybridoma were not accessible or attainable upon request by another. In fact, the Policy Concerning Availability of Materials of the journal of *Cancer Research* would suggest that to the contrary of Applicants' assertion, the antibody and the hybridoma were at least attainable by another upon request. Applicants' arguments have been carefully considered but not found persuasive.

Double Patenting

45. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

46. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

47. Claims 64, 65, and 71 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 12, 23, and 24 of U.S. Patent No. 6,274,143-B1 in view of WO 94/11508-A2.

WO 94/11508-A2 teaches methods for producing anti-idiotypic chimeric antibodies that bind specifically to the paratope of anti-HMFG antibodies (pages 33 and 34, Example 12; pages 42 and 43, Example 29). Furthermore, WO 94/11508-A2 teaches that such anti-idiotypic antibodies are suitable for immunizing humans against neoplasias, i.e., cancer (page 1) and teaches methods for treating humans with immunogenic compositions comprising the chimeric antibodies (claim 54, for example). WO 94/11508-A2 also teach methods for making and using cloning and expression vectors, which comprise polynucleotide sequences encoding the light and heavy chains of the antibodies, and methods for making and using host cells comprising such cloning or expression vectors (claims 31 and 40, for example).

Although the claims of '143 are not drawn to a polynucleotide encoding an polypeptide comprising the variable domains of the light and heavy chains of monoclonal antibody 11D10, in view of the teachings of WO 94/11508-A2, it would have been obvious to one of ordinary skill in the art at the time the invention was made that polynucleotides encoding a recombinant single-chain antibody derived from the amino

acid sequence of monoclonal antibody 11D10 could be made and used to produce immunogenic antibody or alternatively, to directly immunize a mammal with the polynucleotides to elicit an anti-HMFG immunological response in the mammal directed against the antibody encoded thereby.

Conclusion

48. No claims are allowed.

49. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

EP 0088994-A2, US Patent No. 4,642,334-A, Ibrahim, et al, Roark, and Monestier teach the polynucleotide sequences of isolated nucleic acid molecules that does not anticipate the subject matter of the claims and therefore could not be used as a bases for rejections of the present claims under 35 USC §§ 102 and/or 103. Nonetheless, it is noted that each reference teaches the polynucleotide sequence of an isolated nucleic acid molecule that is identical to a region of at least 100 contiguous nucleotide residue of the polynucleotide sequence set forth in SEQ ID NO: 1, except for a mismatch at position 224 of SEQ ID NO: 1, which could become relevant if a sequencing error is later discovered by Applicants.

Zeytin, et al and Gavilondo, et al are pertinent to the claimed invention and demonstrate the state of the art. Bodey, et al discuss the reasons for the lack of success in immunotherapy.

50. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
March 18, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600